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INDUSTRIAL HYGIENE IN THE NATIONAL DEFENSE PROGRAM *

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TODAY it is acknowledged that military mobilization and expansion are impossible without industrial mobilization and expansion. We know that steps to perfect the Nation's industrial mobilization are being taken every day, and that any condition which tends to retard efficient production of defense materials is considered of major importance.

We know that the industrial expansion *now* in progress brings in its wake numerous health problems affecting the working population. Do these health problems have any significant effect on the *rate* and *quality* of our industrial production? If so, what provisions are being made today to solve these problems?

EFFECT OF INDUSTRIAL DISABILITY ON PRODUCTION

Although, today, we know how to control the majority of industrial health hazards, the application of that knowledge lags far behind, so that even in normal times, a large proportion of our industrial workers are confronted with working conditions unfavorable to health and well-being. *Even in normal periods,* the loss of time due to all types of disability in industry amounts to the staggering total of 350,000,000 days a year, or considerably more than 1,000,000 work years a year. This burden confronts the defense program and must be reckoned with in any production schedule. It is realized that these astronomical figures are difficult to grasp. The *monetary* cost alone of this lost time amounts to the overwhelming sum of approximately ten billions of dollars. Compare this with the national debt!

However, if we do not wish to consider these figures in terms of money, nor even in terms of health and welfare, we can at *least* consider them in

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terms of what they mean to our present defense program. Estimates made by the U. S. Bureau of Labor Statistics are available, which show the number of man-hours necessary to produce certain materials vital to defense. The 350,000,000 days lost due to disability among workers, if interpreted in defense materials, are the number of days it takes to build 52 battleships, 164,706 combat tanks, or 107 average size cantonments. If by applying our present knowledge of industrial hygiene to such an extent that we could show a 10 per cent reduction in these time losses, and 10 per cent is a very modest objective, it is evident that we would have done much to eliminate one bottleneck in the defense program which merits serious consideration.

There is yet another factor which must be realized in any discussion of the relationship between industrial health and the national defense program. If we do not today take steps to create safe and healthful working conditions for the workers employed in our defense industries, then we may anticipate that, after the emergency is over, there will be thousands of men and women whose health has been irreparably damaged because of exposure to harmful conditions in those industries. The socio-economic implications of this fact also merit serious consideration.

What then are the specific industrial health problems which we must solve, if we would avoid delay in the defense program and impaired national health after the emergency?

The Problem in Normal Times

Despite years of continued improvement in industrial hygiene, industrial accidents in the United States still cause 17,000 deaths, 75,000 permanent, and 1,400,000 temporary disabilities annually. Recent surveys of industrial plants throughout the Nation show that more than 1,000,000 persons are engaged in work where industrial dusts can create a serious health hazard under certain conditions, nearly 1,000,000 persons are handling lead and its compounds, and another 50,000 are using mercury and its compounds. In addition, many millions of workers are exposed to materials which may produce disabling skin diseases.

Of greatest significance, however, is the enormous waste of life and efficiency resulting from nonindustrial illness among workers. As a matter of fact, the amount of time lost from work, because of ordinary illnesses, is 15 times as great as the total time lost due to accidents and occupational diseases combined. It has also been demonstrated that industrial workers have a higher rate of physical defects than do nonindustrial workers, and that excessive mortality is especially notable among unskilled employees, whose death rate from all causes is 100 per cent or more in excess of the rate among agricultural workers.

These, then, are some of the problems of industrial hygiene confronting our nation in *normal* times.

The Problem in Defense

Needless to say, industrial mobilization in recent months has greatly augmented industrial health problems. Able-bodied men are being drawn into military service and are being replaced in industry by women, young adults, and older men. Many of these new workers are not as physically fit as the men they replace, and many of them, especially women, are unaccustomed to an industrial environment. *Unless* that environment is made safe for these new industrial recruits, and *unless* these workers are made health and safety conscious, we may expect a marked rise in accident and disease rates.

The problem of fatigue, so important in the first World War, will again appear as a result of the speed-up in industrial production. Hazardous chemicals will be used with little or no time to determine in advance their toxic nature. We may expect crowding in many factories, and under the pressure of the emergency, we may expect a tendency to relax that eternal vigilance, so necessary for the prevention of accidents and diseases among workers. Dr. Parran has stated that our industrial machines are rated as the most efficient in the world, and he rightfully insists that the men and women who operate these machines should be given the opportunity to do so with a comparable efficiency.

These, in brief, are some of the industrial health problems facing us today. Have we the organization and the program for solving these problems?

Organization and Program

Fortunately, the groundwork laid by research during the past quarter century, and the organization developed during the past several years for the application of this research by industry and by the States, finds us better prepared to cope with industrial health problems than at any other time in our industrial history. It is universally conceded that the prevention of conditions inimical to health is *always* cheaper and *more* effective than attempts to correct them after they have gained headway. We know that *every* job *can* be done *safely* by applying our present knowledge of industrial hygiene.

Ordinarily, the legal responsibility for protecting the health of our workers is a function of official local public health agencies. In view of the fact, however, that industrial expansion for defense purposes has been instigated by the federal government, the communities where such expansion arises may reasonably expect the federal government to assist them in accomplishing the task of protecting and improving the health and efficiency of the workers in defense industries. Only by so doing may we assure ourselves of an uninterrupted flow of materials so vital for the defense program.

The Organization. The organization which has been effected to achieve this objective may be described as follows. The Health and Medical Committee of the Federal Security Agency, a defense organization, has appointed

a Subcommittee on Industrial Health and Medicine, the duties of which are to advise on the industrial health and medical aspects of national defense. This subcommittee also promulgates policies and suggests means of coordinating all industrial hygiene activities for the national defense.

Within the Federal Security Agency is the U. S. Public Health Service, containing the Division of Industrial Hygiene of the National Institute of Health. The Subcommittee on Industrial Health and Medicine has recommended that the Division of Industrial Hygiene of the Institute assume leadership in achieving the objectives previously cited. This designation is based on the fact that the Division of Industrial Hygiene has more than 26 years of experience in research and related problems, and at present has the personnel, facilities, and relationships with national, state, and volunteer agencies directly concerned with industrial hygiene problems.

Realizing that the responsibility for the protection of the health of our millions of workers lies finally with the states, the Division of Industrial Hygiene of the National Institute of Health, with the aid of funds available under Title VI of the Social Security Act, has organized and developed industrial hygiene services in more than 30 states. The work of these state units is so integrated with that of the Division of Industrial Hygiene that there now exists a nation-wide organization to serve effectively the millions of workers in defense industries.

The Program. On February 17 and 18 of this year, a conference was held for the purpose of developing a nation-wide program in industrial hygiene in defense industries. This conference, sponsored by the Division of Industrial Hygiene of the National Institute of Health, was attended by representatives from the various State industrial hygiene units, the Subcommittee on Industrial Health and Medicine of the Defense Council, and prominent leaders in the field of industrial hygiene.

At this conference, the following pressing problems in industrial hygiene were defined:

1. Further expansion in personnel, facilities, and funds of State industrial hygiene units and of the Division of Industrial Hygiene of the National Institute of Health.
2. Aid to military establishments, upon request of these establishments, in evaluating health hazards, and in the training of personnel.
3. Surveys of commercial shipyards, airplane plants, and establishments producing military vehicles and munitions, and the training of industrial hygiene personnel in these industries as needed.
4. Promotion of first-aid in the construction of industrial plants, especially those in isolated areas.
5. Toxicological investigations of materials vital to national defense, notable among which are toluol, trinitrotoluol, lead azide, and vinyl cyanide.

The conference recognized the importance of environmental sanitation surrounding isolated industrial areas, but was informed that this problem

is being handled by local health authorities with the aid of other divisions of the U. S. Public Health Service.

The program finally adopted by the conference, and one now in effect, envisaged a close working relationship between the Division of Industrial Hygiene of the Institute, the various state industrial hygiene units, and other agencies, both governmental and non-governmental, such as the U. S. Department of Labor, the Council on Industrial Health of the American Medical Association, industry, and labor. The program being applied in each important industrial area has the following objectives:

1. The evaluation and control of the various health hazards resulting from exposure to dusts, fumes, gases, vapors, and other materials.
2. The provision of advisory services to industry in connection with the construction of new plants and the renovation of old plants, so that adequate facilities for health and safety may be included in the plans.
3. The promotion of physical examinations and medical services for the workers, in order that the benefits of preventive and curative medicine may be applied promptly to their individual health problems.
4. The control of communicable diseases among workers through a control program developed in connection with the general public health services of the community.

It is believed that the above program can best be fulfilled by supplementing the facilities of state and local units through the expansion of the services now provided by the Division of Industrial Hygiene of the National Institute of Health. Congress has made available recently additional funds for this work and today there are several mobile units, each consisting of a physician and an engineer, working in key defense industries, in coöperation with the state departments of health. By July of this year it is planned to have approximately 20 such units in the field.

In the work of these mobile units, the engineering personnel are concerned with evaluating the working environment and recommending ways and means for the control of any health hazards revealed by the investigation. The medical personnel, on the other hand, work very closely with local medical organizations, such as the state committees on industrial health developed by the Council on Industrial Health of the American Medical Association. These medical officers appraise present medical control services in industry and recommend improvements in these services, where indicated. The problem of personal relationships, or mental hygiene in industry, is emphasized. Plant management is informed, either directly or through the medical department, if one exists, of the importance of such provisions as periodic inspection and appraisal of plant sanitation and occupational exposures, followed by the adoption and maintenance of adequate control measures; the provision of first-aid and emergency services, and the prompt and early treatment for all illnesses resulting from occupational exposure are also recom-

mended. Impartial health appraisals of all workers and the provision of rehabilitation services for the correction of defects are additional functions of a medical department which are advocated.

The work of the Division of Industrial Hygiene has been aided in many of the defense industries by the splendid coöperation afforded it by the War Department. The Secretary of War, in a circular memorandum dated March 18, 1941, has informed all the branches of the War Department employing civilians for industrial work and for those having direct jurisdiction over contract production, that the Division of Industrial Hygiene of the National Institute of Health has the necessary facilities for effectively rendering services for the protection of workers in these industries. The Secretary of War recommended that full advantage be taken of the services available and has designated the Safety Officer, Office of the Chief of Engineers, to coördinate these activities. As a result of this coöperative program, the Division of Industrial Hygiene of the National Institute of Health has already developed for the Section on Construction, Division of the Quartermaster General, minimum requirements for first-aid rooms and infirmaries in new construction projects.

Time does not permit discussing the many other activities of the Division of Industrial Hygiene in the defense program. Brief mention should be made of the Division's work in the training of personnel recruited for the mobile units functioning in the various states, the preparation and dissemination of both technical and non-technical information on the various phases of industrial hygiene, and the fundamental research work in progress at our laboratories on such substances as toluol, lead azide, and similar compounds vital to the defense program.

Responsibility of the Medical Profession in the Program

In the program for the protection of the health of workers in defense industries the medical profession bears certain responsibilities. First, it is highly essential that physicians inform themselves further concerning occupational diseases, so that they will recognize such diseases more readily in the course of their practice. It is very important that the private practitioner make this effort, in view of the fact that it is now well established that two-thirds of the workers in this country are not provided with either part-time or full-time services at the plant, but must seek such services from their private physicians. The importance of obtaining an accurate and detailed occupational history from a patient cannot be overemphasized, in view of the fact that experience has shown that very often a man's occupation may have a real bearing on his health.

It goes without saying that the physician has a definite responsibility in reporting to the proper authorities the occurrence of occupational diseases among workers coming to his attention. Physicians should adopt the same attitude toward the reporting of occupational diseases, which now exists with

regard to the reporting of communicable diseases. The medical profession can make still another important contribution in the field of industrial medicine, by stimulating the preëmployment and periodic physical examination of workers in industry and by calling attention to the necessity of correcting those physical defects revealed by health examination. And, finally, the medical profession should strive to coöperate with *that* local health agency which is responsible for protecting the health of workers. The private practitioner, either as an individual or through his state and local medical organization, should utilize to the fullest extent the services which may be rendered by the official industrial hygiene division in his community.

In closing, it is desired to emphasize that the industrial hygiene program which has been briefly sketched has been created, not as an emergency improvisation, but as an integral part of our national life in the future. We must not forfeit the gains we have made for the sake of expediency. All of us, be we public health workers, private medical practitioners, engineers, chemists, industrial managers, or factory workers, must assume our share of the responsibility and coördinate all of our efforts, so that the men and women in our industries will attain a high level of efficiency and health.

THE CONTROL OF INFECTIOUS DISEASES IN RAPIDLY MOBILIZED TROOPS *

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ASSEMBLING men from widely different environments, into the close contacts of military mobilizations favors the accelerated spread of infectious diseases and the development of explosive outbreaks. This means that carefully planned procedures for blocking their spread must be weighed against the exigencies of the military emergency. Whenever it is possible, and to the greatest extent possible, we want to counteract the passage of infection from the carrier to the susceptible recruit.

Zinsser [1] and others have suggested a scheme of "gradual mobilization" which would consist of regional aggregations of recruits in small groups of several hundred men in separate local camps for a few months before being concentrated in larger groups in distant areas for longer periods of intensive training. A discussion of the practicability of such an ideal plan would involve military administrative factors which might carry us beyond the scope of this paper. However, the obvious wisdom of this plan, from the medical point of view, requires that it have a prominent place in any consideration of military preventive medicine.

Whatever the method of mobilization, we have certain well tried procedures for use in combating infections. These are: strict examination of all men who are called up or volunteer; immunization; prompt recognition, isolation and treatment of contagious cases; immediate examination, continuous observation, and sometimes quarantine of contacts; rigid maintenance of a hygienic routine; adequate nutrition; and the sanitary control of the environment.

The men who are chosen in the present mobilization are being much more effectively examined than on any previous similar occasion. In addition to care in the detection of the acute contagious diseases serological and roentgen-ray examinations are eliminating many men who would be bad military risks.

The possibility of a rapidly changing and uncontrolled environment makes individual prophylaxis imperative to an Army. In certain directions our means for securing immunization have been refined and extended. In addition to the long established practice of vaccinating every man against typhoid fever and smallpox, many authorities are recommending the routine use of tetanus toxoid.[2] Individual protection through artificially induced immunity will also be given in special cases where circumstances indicate it. Simmons [3] has discussed this subject thoroughly in a recent paper on immunization in the Army. He has pointed out the value, in localized endemic

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outbreaks, of the use of diphtheria toxoid and, in some instances, of scarlet fever toxin. For troops that may be sent to areas in the tropics, we have for consideration the possibility of vaccination against cholera, plague, and typhus fever. The War Department directed in February (1941) "that commanding officers take immediate action to vaccinate against yellow fever all military personnel now stationed in the tropical regions of the Western Hemisphere, including Panama and Puerto Rico." [4] The vaccine will also be given to all personnel ordered to those regions prior to their departure.

Although the long struggle to secure an effective vaccine against yellow fever has at last yielded excellent results, we still have the great challenge of the need for specific protection against a number of other serious infections, notably influenza. A board has recently been established by order of the Secretary of War for the investigation of influenza and other epidemic diseases in the Army. This board will "make immediate arrangements to utilize every scientific facility available in a concerted effort to control these diseases and to reduce their mortality to a minimum." [5] In my opinion the establishment of the various commissions, functioning under this board, is the most significant and important step ever taken by any Army to achieve the control of military disease hazards. We have apparently escaped a major epidemic of influenza this year, but this good fortune is only a reprieve. It seems highly probable that we shall be subjected to another pandemic in the not far distant future. The time available, before it comes, is being used to push vigorously the intensive research, already under way, on methods for improving our means of combating this disease whose devastating effects are aggravated by emergency mobilization.

Other illnesses, against which protection for men living under field conditions may be needed, are: measles, mumps, meningitis, relapsing fever, malaria, gas gangrene, syphilis, and gonorrhea. The diseases which take epidemic form will receive special study by investigative teams which will be sent by the Surgeon General for temporary duty at military stations where and when there is a need. These teams are part of the organization referred to before in connection with the establishment of the board for the investigation of influenza and other epidemic diseases in the Army.

Syphilis and gonorrhea, which have always been responsible for serious loss of time and military effectiveness among troops are being better controlled than at any previous time. There are several reasons for this. One is an increase in the understanding of the diseases by the men themselves. Another is the changed attitude of higher authority and of medical and administrative officers generally in the matter of punishment. At present the infected soldier loses pay while he is away from duty because of his disease, but suffers court-martial only if he fails to report for treatment. Improvements in technic and drugs for therapy will lessen materially the loss of time and the sequelae of gonorrhea and syphilis during this mobilization.

Venereal disease is, of course, a civilian contribution to our armed forces. Therefore the organization of the home front defense against these major

causes of disability by Surgeon General Thomas Parran is a source of profound optimism. Working in close coöperation with the Army commanders, with the American Social Hygiene Association, local health, welfare and public safety officials and all other interested groups and individuals, a coördinated plan is already functioning which will reduce the sources of syphilitic and gonorrheal infection among our troops. Moreover the work initiated during this mobilization will have a lasting effect. The administrative innovations and the scientific research made possible by the concentrations of men in camps are merely the result of an acceleration of the country wide campaign initiated some years ago by the Surgeon General of the Public Health Service to rid our land of one of its most depressing shadows. The Army will take full advantage of this opportunity to aid in speeding up this great work.

The more highly efficient methods for immediate diagnosis and especially for treatment will result not only in lowered mortality from the acute infectious diseases, but will also serve, it is believed, to reduce the incidence of infections. The latter may be accomplished through shortening the duration of exposure to the sick and through a curtailment of the infectiveness of carriers. Everyone knows how completely the sulfa-group of drugs is changing the attitude of our internists toward severe infections due, notably, to virulent streptococci, pneumococci and meningococci. Physicians are confident now that a high death rate will result only from some interference with early treatment.

Other factors which will help in improving resistance to infections are the greatly enlarged knowledge we now have of nutrition and the channels provided for the application of that knowledge. A sub-committee of the National Research Council has been dealing since early in July 1940 with the nutrition problems of the Army and Navy.[6] Our Army is already the most abundantly fed in the world, but it is believed that centrally regulated menus to assure a balanced ration, the more precise specifications for vitamin requirements, and improved forms of concentrates now available, will result in higher resistance to disease and greater physical endurance. Vitamin B fortified flour and bread, and vitamin D enriched pasteurized milk are examples of the products already in use.

Although we derive so much assistance from these measures which help in producing and increasing both specific and general resistance to infections, we still have to rely on rigidly controlled environmental sanitation in attempts to avoid the most serious of the health hazards which arise during the training period. The group of diseases which take heaviest toll among those for which we have no specific immunizing agents are the upper respiratory infections—bronchitis and pneumonia, both primary and secondary to influenza, measles and other diseases. Of the grand total of admissions for disease in the Army during 1918, and 1919, bronchitis, pneumonia and influenza represented one-third, and were the cause of 80 per cent of all deaths due to

disease. In addition to these three, every medical officer knows of the tremendous loss of time and the expense and suffering resulting from outbreaks of common cold, tracheobronchitis, measles, mumps, and meningitis. It will be noted that every one of these diseases may be spread through the air. Our ideas concerning the spread of infection by droplets containing infectious material from the nose and throat have undergone marked changes as a result of the researches of William Firth Wells in regard to air-borne infections. Although no doubt respiratory infections are spread by the large droplets examined by Flügge [7] in 1898, the range of transmission of these larger droplets is limited strictly by the force of gravity. That type of spread is not essentially different from direct contact. Wells has demonstrated clearly that the residues of smaller droplets may float in the air for long periods over distances far in excess of those once believed to be possible.[8] These droplet nuclei which form from expelled droplets of 0.1 mm. and less in size may carry infectious material which remains viable for periods long enough to infect other individuals within the enclosure.

Wells has shown that ultra-violet irradiation is lethal to organisms of the droplet nuclei which are in the atmosphere. His well controlled experiments show clearly two things which may hold the key for checking the spread of air-borne infections, namely: (1) infectious agents (for example, influenza virus, streptococci, and other pathogens of the naso-pharynx) do survive in the droplet nuclei which are transported by air currents through enclosed spaces and (2) the air can be disinfected by ultra-violet radiation.

Both of these essential factors—that is, that infection is transmitted through the atmosphere and that the disinfection of the air can be accomplished by ultra-violet radiation—have been demonstrated repeatedly under controlled experimental conditions. Our knowledge of specific requirements for large scale application of this knowledge is being rapidly developed. However, there is enough evidence now at hand to indicate prompt and extensive use of ultra-violet radiation for the disinfection of air where there are concentrations of people as in auditoriums, barracks, and mess halls.

Nobody thinks that radiant disinfection of air is the one and only answer to the control of respiratory infections. It cannot be expected to affect materially those organisms in the large droplets expelled by coughing, sneezing, and talking which can and do infect persons in close contact with the origin of infection. However, ultraviolet radiation, if applied for the proper length of time and in the necessary amounts, is lethal to the infectious material in the droplet nuclei which float about in the air and which can be rapidly dispersed by air currents.

Wells is making a careful study (which is now in its fourth year) of the possibility of reducing the seasonal incidence of measles, mumps, chickenpox, and the other childhood diseases, by sterilization of the air under practical conditions. This work is being done in some of the public schools of Swarthmore, Pennsylvania, and in the Germantown Friends School of Phila-

delphia. His early findings, as yet unpublished, are strongly indicative of the usefulness of ultra-violet radiation in reducing the incidence of air-borne infections in classrooms. That disinfection of the air in army barracks, air-raid shelters, and such places where war and other circumstances force extraordinary crowding of susceptibles in semi-confined atmospheres would be equally or even more effective is a logical inference. In my opinion, there is sufficient evidence already available to warrant the practical installation immediately of ultra-violet lights in structures where mobilized men are quartered, and where they are accustomed to congregate, in order that observations under military conditions may be made.

In conclusion, in so far as the military emergency will permit their application, the following procedures are available to us for the control of infectious diseases in rapidly mobilized troops:

1. Careful examination of every registrant for evidence of such conditions as incipient or latent tuberculosis, syphilis, and other diseases which men may have when selected or enlisted.
2. Immunization against smallpox, the typhoid fevers, tetanus and yellow fever; with extension of individual prophylaxis under specific circumstances against diphtheria, scarlet fever, measles and possibly against influenza.
3. Avoidance when feasible of sudden geographic shifts during seasons in which the incidence of certain diseases such as pneumonia is known to be high.
4. Maintenance of a high quality of hygienic regimen with special emphasis on fortification with vitamins.
5. Avoidance of excessive fatigue and exposure during the hardening period.
6. Continuation of the well-tested methods for the control of the water supply; use of pasteurized milk exclusively; and exacting inspection of meats and other foods.
7. Careful attention to spacing of beds in squad rooms and hospitals and to ventilation with a thorough and open-minded trial of radiant disinfection of the air under controlled military conditions.

At no previous period in the history of our Army has there been available to us so great a variety of effective methods for controlling the morbidity and mortality resulting from infections. Certainly, at no previous period has there been a more efficiently organized plan for the utilization of current knowledge and for the expansion of such knowledge. This is clearly revealed in the following statement made by Surgeon General James C. Magee when he recommended the establishment of the board for the investigation of influenza and other epidemic diseases in the Army: "The establishment of this board will make available to the Army the scientific resources of the country to assist in the program for the control of influenza and other epidemic diseases which will undoubtedly arise in our expanding Army." [9]

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THE MECHANISMS OF PERIPHERAL CIRCULATORY FAILURE*

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ORIENTATION

THE capillaries constitute the keystone of the circulation, in the sense that maintenance of an adequate capillary flow is essential for the proper exchange of respiratory gases, electrolytes and water, foodstuffs and waste products. The rate of capillary blood flow is regulated (figure 1) by the pressure in the small supplying artery (*A*), by the size of muscular arterioles (*B*), possibly by active changes in size of capillaries (*C*), by pressure of surrounding tissues (*D*), by the pressure in the small venules (E), and by the viscosity of the blood itself.

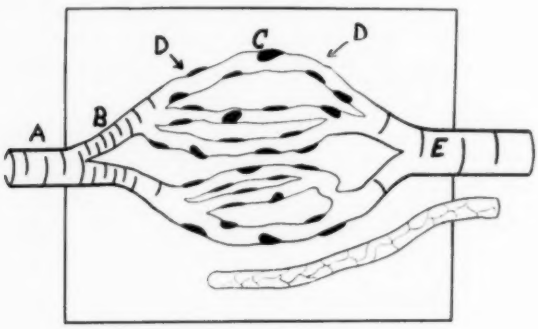

FIG. 1.

Circulatory failure, in its broadest sense, develops whenever the driving pressure in small arteries (*A*) is not adequate to overcome the composite resistance (*B, C, D, E*) offered in capillary districts, and the blood flow therefore decreases. Circulatory failure may exist with normal, low or high arterial pressures. For example, it occurs in chronic congestive heart disease, even while arterial pressures still remain within normal ranges, owing to the high resistance offered by venous pressure at *E*. It develops in conjunction with chronic myocardial depression and follows coronary occlusion, pericardial effusions and Pick's disease, even when arterial pressure is maintained by compensatory constriction. Two peripheral factors operate: the higher venous pressure at *E* and the reduced caliber of vessels at *B*. Circulatory failure occurs during hypertension when the pressure in

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TABLE I

Symptom Complex of Acute Circulatory Failure (Shock)

General Appearance and Reactions	Skin—Mucous Membranes	Circulation	Miscellaneous
Countenance drawn—anxious lusterless eyes sunken eyeballs ptosis of upper lid (slight) upward rotation of eyeball (slight)	*Skin* pale, livid, ashen gray slightly cyanotic moist, clammy mottling of dependent parts loose, dry, inelastic, cold	*Superficial Veins* small, invisible Failure to fill on compression or massage Inconspicuous jugular pulsations	*Respiration* Variable but not dyspneic Usually increased rate, decreased depth Occasional deep sighs
Neuromuscular Tremors, twitchings Restlessness or listlessness Muscular weakness Weak voice Apathy Delayed cerebration Depressed sensibilities Depressed visual and auditory reflexes Depressed tendon reflexes Swallowing difficulty	*Mucous Membranes* pale, livid, slightly cyanotic *Conjunctiva* glazed, lusterless *Tongue* dry, pale, shrivelled, parched	*Heart* Impulse and sounds, feeble Rate, usually rapid *Radial Pulse* Rapid Small volume "Feeble," "thready" *Brachial Blood Pressures* Lowered Pulse pressure small *Retinal Vessels* Narrowed *Venous Blood* Reduced O_2 content Hemoconcentration frequent (?) usual (?) Coagulation time reduced	*Temperature* Apt to be subnormal *Basal Metabolic Rate* Reduced *General but Variable Symptoms* Thirst Vomiting Diarrhea Oliguria

supplying arteries (*A*) is not high enough to overcome the reduction in size of arterioles (*B*). It occurs in various forms of hypotension because the pressure head in *A* is unable to maintain a normal rate of flow through the capillaries. The causes of such hypotension may be: (1) Primary cardiac failure (e.g., sudden profound slowing or acceleration of the heart beat, abrupt development of conduction disturbances, myocardial depression through toxins, anoxia, anesthetics, etc., deletion of contacting fibers as during coronary occlusion and alternans. (2) Secondary cardiac failure due to impairment of ventricular filling as happens in pulmonary embolism, large pericardial effusions, sudden assumption of the erect position, prolonged standing, etc. (3) Generalized arteriolar dilation of central origin (emotional syncope), of reflex origin (epigastric or jaw blows in pugilism) and from interruption of normal sympathetic pathways (splanchnic nerve section, spinal anesthesia).

All of these types are advisedly differentiated from a rapidly progressive form of peripheral circulatory failure, characterized by progressive decline of arterial *as well as central venous pressure* which is designated surgical, traumatic, or toxemic shock.

Symptomatology and Classification

The clinical signs and symptoms of this type of peripheral circulatory failure vary somewhat under different circumstances. They can include any or all of the features gathered from various clinical reports and conveniently summarized in table 1.

Concurrent with development of the views (1899) that traumatic and surgical shock are fundamentally of peripheral origin, internists began to postulate a similar etiological basis for types of circulatory failure that belong more strictly within the province of medicine. The more important associations with various diseases are shown in the following table:

Table II

Causes of Peripheral Circulatory Failure (Shock)

Group I	Group II	Group III
Surgical	*Borderland*	*Medical*
Anesthesia	*Hemorrhage	Infections and intoxications
*Operations	*Gastrointestinal perforations	Diphtheria
*Trauma	Peritonitis	Influenza
*Burns	Pancreatitis	Pneumonia
Exposure	Severe dehydrations	Scarlet fever
Freezing	*persistent vomiting	Meat poisoning
*Strangulated hernia	*diarrhea	*Cholera
*High intestinal obstruction	Gas bacillus infections	*Diabetes
		Adrenal cortical deficiency
		Anaphylaxia (?)
		Thymic death (?)
		Status lymphaticus (?)

* Cases in which loss of blood or plasma plays important, dominant and perhaps sole rôles.

In setting up such a concept of peripheral circulatory failure in medical practice, internists were aware, of course, that acute cardiac disturbances may develop concurrently and that death may be due to primary cardiac or respiratory failure.

The Keystone of Peripheral Circulatory Failure

In reviewing the mechanisms by which such circulatory failure is started and those by which it progresses, it is advisable to begin with facts upon which all seem to agree. Reduced venous return to the heart (decreased effective venous pressure) and capillary stagnation are the *sine qua non* of toxemic and other forms of shock.

It seems paradoxical—but it is true—that the proximate cause of the hypotension which develops progressively is due to diminished cardiac output. This occurs, not because the myocardium is depressed, but because an insufficient volume of blood returns to the heart. Decreased systolic discharge accounts for the feeble heart sounds and apex beat, the decline in blood pressure, the small pulse pressure and the feeble, thready pulse. The empty

peripheral veins are visible evidences of reduced venous return from the limbs.

Possible Causes of the Reduced Venous Return

Obviously, a satisfactory explanation of the reduced venous return would go a long way in explaining the cause of peripheral circulatory failure. Fundamentally, it can only be attributed to two causes: (1) reduction in the circulating blood volume or (2) sequestration of blood in capillaries or sinusoids so that it is virtually removed from effective circulation. Stated in another way, there may be too little blood to fill the vascular system, or the vascular system may be too large for a normal volume of blood.

An actual reduction of blood volume occurs after external or internal hemorrhages; also in conditions in which dehydration, protracted vomiting, prolonged diarrhea, drainage of secretions or of serum from wounds and burns, traumatic damage to capillaries, etc. are a prominent feature. These are demarcated by an asterisk in table 2. However, such loss of fluid is not always obvious in toxemic or infectious types of circulatory failure, with which the internist frequently has to deal. Nevertheless, on the basis of studies on blood volume in animals and man and examination of organs post mortem, many believe that considerable quantities of plasma are abstracted from the blood stream in these conditions, as well. We may accept this provisionally, but reserve the privilege of returning to this phase of the problem at a later time.

The bulk of experimental evidence indicates that when and if such transudation of plasma occurs it is necessarily preceded by capillary stasis and perhaps by intrinsic changes in capillary permeability. Inasmuch as the capacity of the capillary beds is increased, it also acts to withdraw blood from active circulation, thus creating a second way for reducing venous return. We shall, therefore, advance our analysis of the peripheral mechanisms by which circulatory failure occurs if we examine systematically the ways in which such capillary stasis may occur and, if possible, indicate which of these appears the most probable.

Four initiatory mechanisms have been suggested and each can be supported by experimental evidence. They are (1) primary arteriolar dilatation, (2) primary arteriolar constriction, (3) primary atony and dilatation of capillaries and (4) primary failure of some veno-pressor mechanism.

Primary Arteriolar Dilatation

The arterioles are the terminal stopcocks of the arterial tree which regulate the volume flow of blood from arteries into capillaries. Ever since the pioneer experiments of Claude Bernard on the salivary glands, physiological evidence has supported the thesis that arteriolar dilatation increases capillary pressure and volume. Unused capillaries become patent, the filtration and flow of lymph are augmented and the organ or district affected increases in

volume. This is also the fundamental reaction in inflammatory hyperemia. As a result of such arteriolar dilatation, the venous flow from an organ at first increases; but if widespread territories are involved, the arterial pressure declines and venous flow is reduced. Meanwhile a volume of blood equal to that which " bleeds into capillaries " is prevented from returning to the heart. It is not difficult to calculate that such an abstracted volume may be quite sizeable. It can be argued that such withdrawal occurs essentially from the arterial rather than the venous side. However, the question cannot be settled by such theorizing because circulatory conditions are highly complicated. In brief, we may state that the effect of such primary arteriolar dilatation on total venous return depends upon the extent to which compensatory translocation of fluid from various blood reservoirs, such as the spleen, liver, skin, and perhaps the lungs, takes place. Thus, maximal dilatation of arterioles by nitrites leaves the total return flow of venous blood unaltered or may even increase it; whereas, similar dilatation by histamine is said to reduce it.

Primary Arteriolar Constriction

Many, but by no means all, available experimental results suggest that the arterioles are constricted in various shock-like states. Hence, the conclusion that arteriolar constriction is primarily responsible for capillary stasis and reduced venous return.

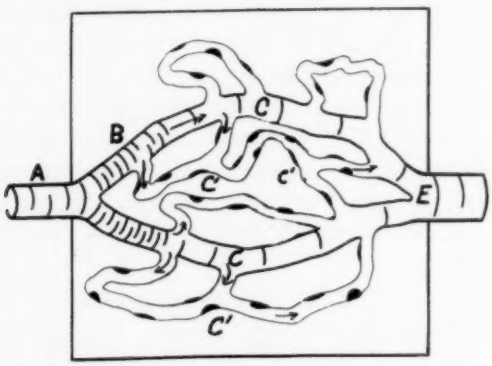

Fig. 2.

Since arteriolar contraction (figure 1, B) primarily reduces capillary pressure and capacity in any territory and shrinks the organ or tissue affected, some mechanism must exist which produces the capillary dilatation. Secondarily, two possibilities exist: (1) The decreased capillary flow following initial arteriolar constriction may cause anoxia or asphyxia in capillaries, which relaxes and increases the permeability of their walls. The concept assumes with Krogh and his school that capillaries have the power of independent contractility; it ignores the evidence of Clark and Clark and of

Chambers and Zweifach that they do not possess such a physiological property.

2. If, as Zweifach [1] has recently claimed, the main nutritional capillaries are not directly interposed between the arteries and veins, as shown in figure 1, but represent a series of shunts, as is schematized in figure 2, an extension of arteriolar constriction to the main A–V capillary (*C*) would shunt blood into the real capillaries (*C*), causing the expansion of those in use and the opening of others not previously in action. It is thus possible, from a dynamic viewpoint, to postulate capillary stagnation after arteriolar constriction either as a passive process or as an active relaxation of capillaries themselves.

Primary Capillary Dilatation

Many chemical substances and tissue extracts, upon intravenous injection, cause circulatory changes which resemble shock. They include certain lymphagogues studied by Heidenhain (extracts of muscles, and crayfish, peptones, etc.), decomposition products or extracts of the intestinal mucosa, liver, muscle, etc., bacterial toxins, snake venoms, histamine, adenylic acid, etc. Most of these are unquestionably capillary poisons which alter the turgor and permeability of capillary walls, thus causing stasis and transudation of fluid. Moreover, various substances such as liver, minced muscle, etc., upon introduction into the peritoneal cavity lead to hemoconcentration, decline in blood pressure, and reveal obvious congestion of capillaries and edema of organs on postmortem examination (Moon). These and other experimental evidences suggest that as yet unidentified chemical substances formed during high intestinal obstruction, rupture or perforation of the gastrointestinal tract, toxins, infections, etc., may act on capillaries in a similar manner and produce capillary congestion, edema, and hence a reduced venous return.

Time is lacking to consider the evidences of guilt or innocence of the various agents suggested. It may be emphasized, however, that failure to identify the substance is not proof of its nonexistence. Indeed, a variety of agents, rather than a common one, may be concerned in various toxic states. It may not necessarily be a single identifiable agent but, as is apparently the case of rennin, may require an activating agent or involve participation of endocrine glands like the adrenal cortex. This would explain the development of similar states of shock during cortico-adrenal insufficiency.

Failure of a Venopressor Mechanism

The ultimate force which returns blood to the heart is, of course, the pressure component still available after blood has been driven through the capillaries. The magnitude of this force is not large; indeed, were it not for a negative pressure within thoracic veins it would not suffice to raise blood to the abdomen in a standing position. The mechanisms by which sub-

sidiary forces aid return is not too clear, but it is commonly believed that they include (*a*) extravascular support offered by elasticity of tissues, contraction and tonus of muscles, etc., (*b*) pumping action of respiration, and, (*c*) active venomotor changes in venules and small veins.

The suggestion that peripheral circulatory failure begins on the venous side of capillary beds presupposes one of two opposite actions:

1. The small venules rather than the capillaries may dilate primarily. This may be due either to a relaxation of their muscular elements and/or to a reduction of pressure in surrounding tissues. Starling [2] and Y. Henderson [3] have both suggested that the decrease in tonus of skeletal muscles during shocklike states may remove such a supporting force. However, most of the evidence suggests that reduction in skeletal muscle tonus could be only of subsidiary importance. Shock does not develop during paresis or myotonia gravis; furthermore stagnation does not appear to occur in limb vessels during toxemic shock. However, cessation of intestinal movements, loss of tonus in viscera, etc. may conceivably be more potent. Granting the operation of such a mechanism, the capillaries would fill as a result of the dissipation of pressure transmitted from arterioles to the tissues.

2. The small venules may on the contrary constrict. This would trap blood in capillaries, increase resistance to pressure transmission and thus diminish the force which returns blood to the heart.

Discussion

The foregoing brief summary indicates the ease with which plausible explanations can be set up to account for the capillary stasis and reduced venous return. It is also possible to prove the correctness of each of these concepts by a judicious selection of experimental evidence. The real difficulty consists in deciding which of the postulated views, if any, is correct. This cannot be done by stating one's own impressions (or prejudices) or by balancing opinions of authoritative investigators. Unfortunately the question can also not be decided by a critical reconsideration of experimental results instead of conclusions based on them. There are enough of these, if accepted at par, to make all of these views untenable. This dilemma may be illustrated by applying experimental facts to the two favored theories regarding the initiating factors in shock.

In order to implicate arteriolar constriction as an initiating factor it is necessary to demonstrate (1) that such constriction exists early in shock and involves widespread areas and (2) that it is of sufficient intensity and duration to cause the sequestration of blood in capillaries. In my judgment, neither has been proved. The experimental evidence that vessels are initially constricted is frequently quoted; that which indicates that they are dilated is conveniently ignored (cf. Bartlett,[4] Morrison and Hooker,[5] Penfield,[6] Forward and Perme [7]). Of the experimental results indicating that constriction

occurs (Erlanger, Gasser et al.,[8] Sollmann and Pilcher,[9] Gesell,[10] Cattell, Jr.[11]), none proves that it is of sufficient intensity to increase the total resistance to the runoff from the aorta. The only evidence we have indicates that peripheral resistance decreases (Dingle, Kent, Williams, Wiggers[12]). Furthermore, experimental and clinical hypertension in which the peripheral resistance is greatly increased, does not eventuate in shock, and no one has succeeded in producing shock by prolonged vasoconstriction following stimulation of afferent nerves. Large unnatural doses of adrenalin, if long continued, lead to shock, but only after withdrawal of the agent. In our experience, the abrupt decrease in coronary flow which occurs when adrenalin injections are stopped often causes death from cardiac, not peripheral, failure. This is also the case when the aorta is compressed for a long time and suddenly released. Freeman[13] reports reduction in blood volume following more reasonable doses of adrenalin, but this could not be confirmed by Hamlin and Gregersen.[14] However, granting such decrease, it remains an inference that vasoconstriction was the cause. Prolonged use of adrenalin has a deteriorating effect on the heart and perhaps on capillaries as well.

To summarize, a critical consideration of existing experimental results does not convince me that primary arteriolar constriction, induced by nervous or humoral mechanisms can be an important initiating factor in peripheral circulatory failure.

It remains to square this conclusion with the obvious constriction of surface vessels which gave rise to the vasoconstrictor concept of shock among clinicians. We may accept such constriction as demonstrated beyond question. However, attention may be directed to the fact that a similar constriction accompanies many forms of visceral pain which do not ordinarily eventuate in shock, among them, gastric, biliary and ureteral colic. Furthermore, admitting a degree of constriction in skin and muscles to the point of tissue asphyxiation, it is curious that the pathological changes in capillaries described as characteristic of shock are not found in somatic structures. Obviously, the scientific evidence does not fit together in implicating vasoconstriction as a cause of capillary stasis.

Dilatation of capillaries through humoral agents, followed by transudation of plasma must certainly be considered a probable mechanism in forms of shock in which obvious loss of blood or fluid cannot be held accountable. It is necessary, however, to make certain reservations with regard to the probable agent. The unknown agent (or agents) must be potent and exert a sustained action; it must affect rather extensive capillary territories and must also have a certain selectivity, for the somatic capillaries are apparently unaffected.

Personally, I challenge a common view that anoxia or asphyxia of a degree which is probable, could produce the severe reactions. Prolonged anoxia, e.g., at high mountain tops, produces very serious symptoms in animals and man, but not those of shock. The extreme passive congestion of viscera attending chronic heart disease is attended by a marked anoxia for

many years without evidence of shock. Recent observations of Maurer [15] have proved that general anoxia increases lymph flow, but inasmuch as, in the body, this is returned by lymphatic ducts to the venous stream, such increased transudation cannot contribute to the reduced venous return.

It is profitable to reconsider whether the circulatory volume is as significantly reduced in toxemic shock as is commonly believed. The idea—a very old one—was suggested by the apparent thickness of the blood after death from certain forms of shock, e.g., after cholera. It was supported by data that the specific gravity, plasma protein, red cell counts and hemoglobin increase in various forms of shock. It is supposed to have been demonstrated beyond question by use of dyes and other substances, suitable for determining blood volume. Results so obtained must be relative rather than absolute, since dyes and other colloidal substances would pass through leaking capillaries and involve an error unless they were returned by lymphatic channels to the circulation. Furthermore, the translocation of blood from various depots has not been adequately considered. Gregersen informs me that, in his experience, blood volume determinations are treacherous unless animals have been previously splenectomized. How much of the hemoconcentration now regarded as an index of depleted plasma volume is due to addition of red corpuscles from the spleen and surface capillaries rather than abstraction of plasma through capillary walls?

The evidences of edema and serous effusions on autopsy would seem to constitute the most conclusive evidence that circulatory fluid is lost. But such studies are qualitative only; they cannot tell how much plasma is lost. It is impossible to measure or calculate the volume of edema fluid in tissues and compare it with the compensatory volume placed in circulation by contraction of the spleen, skin vessels, etc., not to mention fluid reabsorbed in other regions. The suggestion that some of the edema seen in tissues, post mortem, may have developed during the process of death or even after death, will perhaps sound fantastic to pathologists. However, it ought to be made and investigated, particularly since pulmonary edema and large serous effusions are seen so commonly on autopsy, while signs of their occurrence are strikingly absent during the course of experimental or clinical shock. Have clinicians missed important signs of shock or do the autopsy findings show conditions which did not exist during life?

A few words may be added in regard to the concept that arteriolar dilatation represents an initiating event. The concept has been generally abandoned, largely because it had become so definitely linked with the theory of failure or exhaustion of the vasomotor center. The latter appears to have been definitely disproved. However, it is not necessary to assume, particularly in toxemic forms of shock, that arteriolar dilatation is necessarily dependent on failure of a central or peripheral nervous mechanism; it could be caused by action of the same humoral agents which are generally believed to act on capillaries. Indeed, it is not improbable that, if any such agent exists, it would affect arterioles, capillaries and venules alike. Sir Thomas

Lewis, with greater wisdom than shown by others, refers toxic actions to the "minute vessels," which presumably include arterioles.

The argument that primary arteriolar dilatation is excluded by the fact that decrease in cardiac output precedes the fall in blood pressure is not a valid one. It is conceivable, and indeed probable, that primary dilatation in fairly extensive regions would be compensated, *pari passu*, by cardiac acceleration and arteriolar constriction in other regions through sinus caroticus and aortic reflexes. This happens very quickly in normal subjects after inhalation of amyl nitrite; pressures are restored in 1 to 2 minutes, while vessels remain dilated in certain regions. Compensatory constriction might operate to do more than restore a normal total aortic resistance. Enough blood may be mobilized from the spleen, liver and skin so that it not merely compensates for any local reduction in venous flow from organs involved, but it may even supply a larger return volume for the accelerated heart to pump. Failure to grasp the many-sided factors involved in dynamic adjustment of the circulation has been responsible for much illogical discussion on the part of investigators not sufficiently familiar with elementary aspects of hemodynamics. According to this conception, a different rôle would be assigned to the generalized constriction of skin vessels during peripheral circulatory failure. They probably constitute a compensatory mechanism by which blood from the skin plexuses is placed in circulation in the viscera rather than being a provocative cause of shock itself.

A few in my audience may recall that similar conclusions were reached as a result of personal investigation [16] of traumatic shock in 1918. With broader experience, I am ready to grant that the thesis that shock is initiated by a primary vasodilatation was not as crucially demonstrated as I then believed. However, the changes in the form of aortic pressure pulses then presented have never been controverted, or explained more satisfactorily. I hold no brief for this or any other conception as to the factor which initiates peripheral circulatory failure, but insist that it is scientifically inadvisable to cast the hypothesis aside too hastily.

Initiating, Sustaining and Precipitating Factors

Following a suggestion of Gesell,[19] it has become customary to differentiate between initiating and sustaining factors in shock. In addition, we must consider the probability that there may be a precipitating factor which determines whether the changes inaugurated and sustained lead to recovery or death. All experimenters who have investigated the shock problem in animals can attest to two impressions: (1) After application of a procedure designed to produce shock, animals may display a moderate imbalance of the circulation for hours. From this they either recover completely or quite suddenly go into a state of irreversible circulatory failure. (2) A standard laboratory procedure which produces shock in the majority of animals, fails to do so in a considerable number. The question, therefore, logically arises

whether in our zeal to implicate capillary stasis, reduced venous return, decreased circulation volume, etc., we may not have overlooked precipitating factors which may not involve the peripheral circulation at all, or only indirectly.

Recent advances in our understanding of circulatory regulation have shown the existence of many mechanisms by which the circulation adjusts itself in health and disease so that arterial pressure is maintained at reasonably standard levels and blood flow is adjusted to the needs of various tissues in different states of activity. These comprise both direct and reflex actions. Additional and hitherto unsuspected mechanisms operating toward these ends are still in the process of discovery. Without prejudice to the view that capillary stagnation, transudation and decrease in circulating volume initiate the changes responsible for peripheral circulatory failure, the possibility ought to be investigated whether a failure or incoördination of the numerous stabilizing mechanisms may not constitute a vital precipitating factor. I understand that this project is under investigation in other laboratories by workers trained in the technic of such studies. These are among the encouraging signs that a shift in emphasis has begun in the experimental study of the problem of peripheral circulatory failure.

Aided by a grant from the Commonwealth Fund, our laboratory has likewise initiated investigations in these directions. It would be premature and wearisome to enlarge upon all the trends of approach that have suggested themselves. However, we may briefly indicate one trial approach which intrigues us at the present time. Preliminary experiments recently reported by Werle and Cosby [17] showed that when the blood pressure of a dog is kept at a level of about 65 mm. for 2 hours or more by bleeding or plasmapheresis, reinjection of all the fluid abstracted may either eventuate in complete recovery or, after very temporary benefit, may result in complete circulatory collapse. A study of the forms of the aortic pressure pulses in dogs that fail to recover suggests that either the natural myocardial or aortic reactions to a restored circulatory volume may have defaulted. Consequently, we are reinvestigating the possibilities that the mechanisms which adapt aortic size and elasticity to varying volumes and pressures of blood, or aberrant responses of the myocardium following prolonged diminution of coronary flow may be at fault.

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THE PNEUMONIA OF FRIEDLÄNDER'S BACILLUS*

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THAT Friedländer's bacillus may be the cause of massive infections of the lung was first pointed out in 1882 when its discoverer assigned to it the chief etiological rôle [1] in the pathogenesis of lobar pneumonia. The expansiveness of this conclusion immediately precipitated a controversy [2] which at the present time seems unnecessarily acrimonious since the statement erred not so much in principle as in accuracy, requiring, therefore, merely modification, and not rejection as recommended on the ground that the organism is involved in pneumonia only in the capacity of a secondary invader. It was Weichselbaum [3] who subsequently clarified the dispute when confirming the concept of earlier workers that pneumococcus is indeed the most frequent agent in primary pneumonia; he nevertheless demonstrated that Friedländer's bacillus may also induce a similar pulmonary condition, but in considerably reduced ratio. This constitutes today the universally accepted concept, although occasional investigators [4] still prefer to regard Friedländer's bacillus in the light of a subordinate rôle (i.e., either as a secondary invader or as a participant in pneumonia metastatic to infection elsewhere). The pertinent literature that has since accumulated is comprised for the most part of individual case reports or at best of small groups of cases. Notable exceptions, however, are the reports of Zander [5] whose bacteriological data are too limited to be entirely authentic, Belk [6] whose observations are essentially histological, but excellent, and Solomon [7] and Bullowa, Chess and Friedman [8] both of whose publications are detailed, thorough, and convincing.

The writer's interest in this variety of pneumonia dates back to 1923.[9] Since then a relatively large number of patients has been studied from the bacteriological aspect and it is desirable at this time to place the observations on record. The strains isolated from these patients have been typed according to the classification devised in 1926,[10] as reported to some extent in 1930.[11] In addition, this communication will include a discussion of the clinical manifestations, statistics, histology, bacteriology, and a brief word on the therapy of the pneumonia of Friedländer's bacillus. The report will serve the dual purpose of recording personal observations and reviewing related publications of other workers.

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Frequency of Pneumonia Due to Friedländer's Bacillus

The pneumonia of Friedländer's bacillus occurs sporadically, although a single report records an outbreak approximating epidemic proportions. Thus, on this one occasion [5] the infection occurred in a labor camp in Germany afflicting 411 individuals from December 1916 to April 1917. The evidence submitted, however, is bacteriologically scanty and clinically it suggests pneumococcus rather than Friedländer's bacillus as the incriminating organism in a certain proportion of the cases, at least. Usually the disease is encountered in adult life and most frequently during middle age or even later, with a tendency to predominate in males. The predisposing influence of alcoholism on this kind of pneumonia has been stressed by numerous

Table I

The Frequency of Friedländer's Bacillus in Human Pneumonia

Investigator	Date	Total number of pneumonias	Incidence of Friedländer's bacillus	
			Numerical	Percentage
Weichselbaum [17]	1886	94	5	5.3
Netter [18]	1892	95	11	11.5
Fraenkel [19]	1908	77	2	2.6
Eyre [20]	1910	102	6	5.8
Lord [21]	1915	192	6	3.1
Avery et al.[22]	1917	480	3	0.6
Cole [23]	1928	183	7	3.3
Habbé [24]	1929	131	5	3.8
Heffron and Varley [25]	1932	716	7	1.0
Sutliff and Finland [26]	1933	1,364	16	1.2
Bhatnagar and Singh [27]	1935	100	13	13.0
Bullowa et al.[8]	1937	4,416	50	1.1
Cecil [28]	1937	4,310	33	0.7
Solomon [7]	1937	5,000	32	0.6
Totals		17,260	196	1.1

authors, as has also trauma, etc., but in the opinion of this writer the cases in which such factors are present are not sufficiently numerous to establish a causal relationship. The writer has never seen an example of this pulmonary disease in infants or children, and the scarcity of references in the literature illustrates clearly its extreme rarity in the lower age groups.[12–16]

A study of the statistics available in the literature indicates that Friedländer's bacillus is responsible for only a small proportion of the total pneumonias. While it is obviously unnecessary to collect all the data bearing on this subject, since it is desirable merely to point out a principle, statistics have been collected from several selected sources in order to convey a general idea of its frequency. Thus, it will be seen from the material assembled in table 1 that varying with the different authors selected, Friedländer's bacillus causes from 0.6 per cent to 13 per cent of all the pneumonias. If, however, all the figures are combined, the composite statistics reveal that of 17,260

pneumonias totaled, 196 were ascribed to Friedländer's bacillus or, stated in another way, this organism occurs in pneumonia in a frequency of roughly one in 100, admittedly a low proportion.

Fatality of the Pneumonia of Friedländer's Bacillus

The low incidence of pneumonia associated with Friedländer's bacillus is more than compensated for by its extremely high mortality, so that while the infection is infrequent, it must be considered as serious. In order to display at a glance the fatality of the disease, statistics have been collected and summarized in table 2. While the data thus assembled do not include

Table II

Collected Statistics on the Mortality of the Pneumonia of Friedländer's Bacillus

Investigator	Date	Number of		Percentage mortality
		Total cases	Fatal cases	
Kokawa [29]	1904	9	9	100
Stülhern [30]	1904	10	7	70
Apelt [31]	1908	10	8	80
Lord [21]	1915	6	6	100
Sisson and Thompson [32]	1915	4	3	75
Zander [5]	1919	411	114	28
Belk [6]	1926	18	18	100
Cole [23]	1928	7	5	71
Kornbloom [33]	1928	4	1	25
Kliewe [14]	1930	11	2	18
Olcott [34]	1933	6	6	100
Bhatnagar and Singh [27]	1935	13	12	92
Bullowa et al. [8]	1937	39	32	82
Solomon [7]	1937	32	31	97
Present Report		55	45	82
Miscellaneous single cases [12–16, 35]		18	15	83
Totals *		653	314	48
Totals corrected for Zander's cases (see text)		242	200	82

all possible references bearing on the subject, they nevertheless suffice to indicate clearly the severity of the disease. Analysis reveals that the mortality has been reported as varying from 18 per cent to 100 per cent. The three examples of low fatality can be explained on the following grounds: the infections observed by Kliewe [14] were in children whose susceptibility, judged by incidence, at least, is extremely low; those reported by Kornbloom [33] represent an example of unfortunate sampling, because the three surviving patients progressed from the more acute to the chronic stage of the disease, a less common termination of this form of pneumonia, as will be described below; while the etiology of Zander's [5] cases is not entirely clear, as already explained. In any case accepting these three references on their face value, the collected statistics indicate a total of 653 pneumonias due

to Friedländer's bacillus, and of these 314 were fatal, giving a composite mortality of 48 per cent. If, however, correction is allowed for the numbers submitted by Zander,[5] the mortality rate rises considerably higher to 82 per cent. Thus it is obvious that the fatality of Friedländer pneumonia is three to four times that seen in pneumococcal pneumonia when untreated with specific antiserum or sulfonamide drugs.

Clinical Manifestations of the Pneumonia of Friedländer's Bacillus

The clinical manifestations of this condition have been described by a number of workers.[1, 5, 7, 8, 21, 30, 31, 36] Nevertheless, it seems desirable to consolidate existing information with personal observations in a brief running account. The clinical classification of Friedländer pneumonia falls conveniently into three variations—lobular, lobar, and chronic. The most frequent occurrence is an acute, abrupt onset, usually with chill, sharp pain, cough, and fever of variable intensity, but more frequently low (102° F. or less). Sputum is usually plentiful, blood-tinged, or rusty, and highly tenacious; its mucoid character together with an excess of blood, often gives to sputa the appearance of reddened tapioca. This is considered as typical of Friedländer's bacillus, but the writer finds no consistent difference between sputa from pneumonia of Friedländer's bacillus and that due to the pneumococcus.

The lobular or bronchopneumonic variety is apparently the least frequent of the pneumonias associated with Friedländer's bacillus. The lesions in this type are essentially scattered and lobular. It may occur purely as bronchopneumonia or conjointly with the lobar form. The most common of the varieties of infection appears to be the lobar, or what some authors prefer to call the pseudolobar form. The consolidation shows great variation anatomically, from localization in a single area in a single lobe to extension throughout one or more lobes and even to involvement of the second lung. Despite numerous attempts to differentiate the lobar pneumonia of Friedländer's bacillus from that of pneumococcus, the writer feels that the clinical similarity between the two is remarkably great, and that usually, the differentiation comes in the nature of a surprise from the laboratory report on the bacteriology of the sputum or blood.

The chronic form of Friedländer pneumonia occurs either as such from the beginning or as a sequel to the acute disease. The former variety is the more common and its onset is slow and insidious, while in the latter, it is initiated in relatively rapid time (five to ten days) by changes in the lung tissue consisting of necrosis and abscess formation, sloughing and cavitation and finally if healing sets in, fibrosis. Thus an occasional patient recovering from the acute phase may pass transitionally into a "chronic pneumonia." Irrespective of its origin, however, the chronic condition eventually becomes clinically indistinguishable, and is characterized as an

exacerbative condition complicated by bronchiectasis and strongly resembling pulmonary tuberculosis. Frequently the continuous absence of acid-fast organisms in the sputum is the first suggestion of Friedländer infection. This form of infection first pointed out by Apelt [31] was studied with great care by Belk,[6] who particularly emphasized its similarity to tuberculous infection, as others have since agreed.[35 e, f, h, i, 37] In this condition the patient may survive indefinitely without great inconvenience or discomfort, as illustrated especially well by the patients described in Collins' [37] report.

In general the disease is relatively short, the duration averaging close to a week. Recovery may be by lysis or crisis, the former apparently predominating. The presence of bacteremia shows great variations, depending upon the different investigators. Thus, of the more recent workers, Cole [23] obtained positive cultures in three of seven patients; Olcott [34] in four of six; Bhatnagar and Singh [27] in three of 13; Collins [37] in one of four; Bullowa, Chess and Friedman [8] in 27 of 41; and Solomon [7] in 19 of 27. This makes a combined total of 57 out of 98 patients (ca. 60 per cent) having bacteremia. Our own experience reveals that approximately half the patients whose blood is cultured ante mortem have bacteremia. Yet at postmortem examination, the large majority of patients will show the organism in blood cultured from the heart, indicating at least an agonal, if not postmortem invasion of the organism into the circulation. Another interesting observation clinically is that the severity of the infection is not necessarily reflected in the clinical condition, the patient frequently appearing in relatively good condition until shortly before death.

It is of further interest that extension of the infection to other organs or tissues is more or less infrequent. One of the patients observed in this series showed meningeal signs, and the spinal fluid was purulent and contained the same organism (Type A) as previously isolated from the sputum. Solomon [7] reports three similar examples in his group of cases.

The blood counts as a rule tend toward a leukopenia, although exceptions are encountered. The shift in white cells is toward the mononuclear elements (lymphocytes and monocytes) at the expense of the polymorphonuclear cells. Sharp decreases in the white cells are usually of grave import. Except for an occasional secondary anemia, the red cells appear to be unaffected.

Roentgenographically, the pneumonia of Friedländer's bacillus has been the object of a special study by several workers.[33, 35 e, f, 38] Kornbloom [33] describes the disease by this method as a progression of four stages: bronchopneumonia, pseudolobar pneumonia, multiple abscess and cavity formation, and finally healing and fibrosis. However, the consensus of opinion appears to be that in the acute lobar form, roentgenograms are difficult to distinguish from those taken during pneumococcal pneumonia, whereas in the chronic type of infection when cavitation has set in, its distinction from tuberculous

disease is not a simple matter, although the cavity walls appear to be particularly thin.*

Histology of the Pneumonia of Friedländer's Bacillus

The histological changes in the lung due to Friedländer's bacillus are more characteristic of the organism than are the clinical manifestations. Histological discrepancies are found in the literature, apparently due to the fact that the descriptions given are based on single cases, which frequently reveal predominantly one or another variation of the infection at the expense of the general and more commonly encountered changes. A number of reports, however, contain accurate descriptions.[1, 6, 29, 30, 31, 32, 34] As in the case of the clinical manifestations discussed above, it seems profitable to give a composite picture of Friedländer pneumonia as reported by others and as seen in some of the patients observed in this study. The infected lung is usually voluminous, heavy and consolidated. The cut surface while granular or uniform, is covered with a tenacious exudate which scrapes off on the surface of a knife as a viscous mixture of blood and pus. The distribution of the lesions may be lobular, lobar or both and may sometimes represent a confluence of separate areas of pneumonia. The tissue is for the most part congested and edematous, with the surrounding bronchial glands often swollen and hyperemic. The tissue may be soft, frequently revealing areas of necrosis with beginning or advanced cavitation. Frequently the latter changes are visible grossly, but when undetected by the unaided eye, they are usually to be seen microscopically, so that this progression of tissue destruction constitutes one of the chief distinctions from pneumococcal pneumonia. When infection involves more than one lobe, the pleura of the interlobar septa become adherent and always thickened. Microscopically, the alveoli are greatly distended and filled with an exudate consisting of varying amounts of fibrin, red blood cells, mononuclear, polynuclear and epithelial cells. The alveolar walls are thin, sometimes even completely destroyed; the capillaries are congested; and the pleura may be thickened and edematous. The organism apparently grows more or less unrestrainedly, so that it is found with comparative ease under the microscope both intra- and extracellularly. The greater part of the phagocytosis is apparently taken over by monocytes. There are obviously variations and exceptions from the picture described, so that the description given must be regarded as conforming to that seen most generally.

* It perhaps goes without saying that just as streptococcus and pneumococcus may become secondarily responsible for a pulmonary condition superimposed on preëxisting respiratory infection (e.g. influenza), so also Friedländer's bacillus is occasionally encountered as the chief agent in pneumonia successive to previous disease. Since the "secondary" pneumonia is similar to the "primary" pneumonia, there is little reason for repeating descriptions.

Histories Illustrating Friedländer Pneumonia

In order to illustrate the general comments made on the clinical, roentgenological, and histological manifestations of Friedländer pneumonia, the histories of two patients are summarized as typical examples.*

Case 1. Patient F. G. was a white male aged 50 years. Until the day of admission, the patient had been in good health. On that day, he complained of chills and fever, productive cough with blood-streaked sputum, and pain in the chest, all of which appeared abruptly and more or less simultaneously. On physical examination, the patient was found to be acutely ill, with a fever of 104° F., and with signs of consolidation over the right upper chest. A clinical diagnosis of lobar pneumonia was made and accordingly 120 grains of sulfanilamide were prescribed daily. The clinical condition became progressively worse and the patient died on the fifth day of illness. In the meantime, roentgenograms revealed a homogeneous density over the right upper lobe, without sign of abscess or cavitation. Laboratory examinations disclosed the white blood cells reaching 9,500 per cu. mm. with 60 per cent polymorphonuclear cells, 30 per cent lymphocytes, and 10 per cent monocytes. Blood cultures were sterile, while the sputum contained a predominance of Friedländer bacilli. At post mortem, the right upper and lower lobes were covered with a fibrinopurulent exudate and the lung weighed three times more than the left lung (unaffected). The infected lung was almost completely consolidated, and the gross and microscopical diagnosis of lobar pneumonia was justified. Bacteriological studies at this time revealed pure cultures of Friedländer's bacillus from the consolidated lung and the exudate.

Case 2. Patient A. G. was a white male, aged 56 years, apparently normal until three months preceding admission to the hospital. At this time, he complained of a productive cough, with sputum which was not blood-streaked. There was pain in the right lower chest anteriorly, shortness of breath, progressive weakness, and loss in weight of eight pounds. Physical examination revealed fever (100.2° F.), persistent cough, signs of consolidation over the right lower chest, and clubbing of the fingers. A clinical diagnosis was made of bronchiogenic carcinoma. Roentgenograms disclosed a homogeneous density over the entire right upper lobe and probably involving a portion of the middle lobe except for an area of radiolucency along the periphery from the clavicle to the fifth interspace. On lateral view the radiolucent areas suggested cavities. Further roentgen-ray study was recommended because of the difficulty of differentiating between bronchiogenic carcinoma and pulmonary tuberculosis. The patient failed rapidly and died on the fifth day following admission. Because of the mistaken diagnosis, no laboratory examinations were made. At post mortem, the true nature of the disease revealed itself as a chronic suppurative pneumonitis with extensive abscess formation and multiple cavitation. Cultures from the lung justified the postmortem diagnosis of chronic Friedländer infection.

Figures 1 and 2 are submitted as supplementary to the histories briefly reviewed above.

* The clinical histories, roentgenograms and histological sections were obtained from the Philadelphia General Hospital where the writer began his studies on Friedländer's bacillus. It is a pleasure to acknowledge the assistance received from the staff, particularly, Drs. P. H. Clark, Harrison F. Flippin, S. Brandt Rose, and the late Robert G. Torrey.

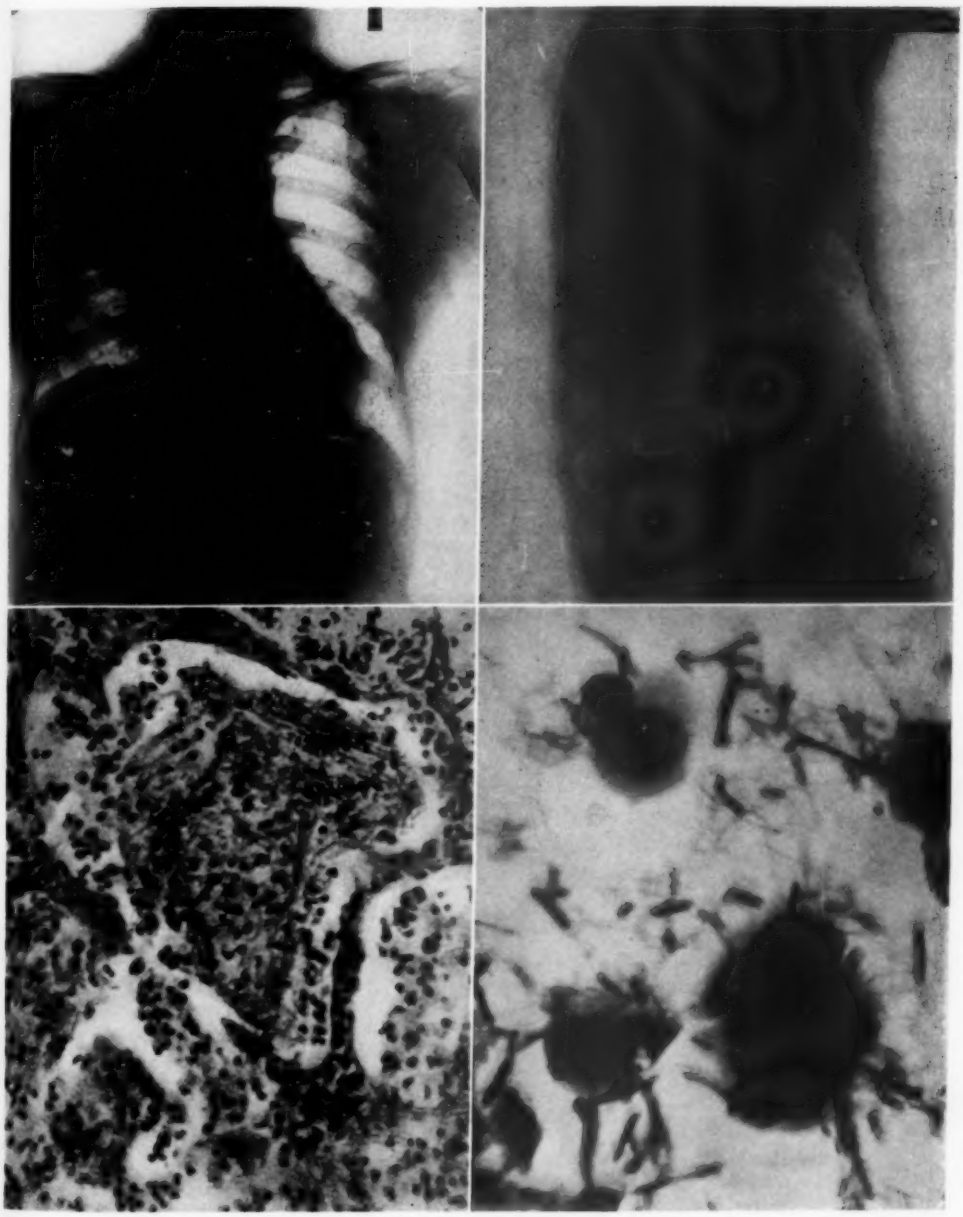

FIG. 1. Illustrations to supplement history of patient F. G.

Upper left: Roentgen-ray photograph of chest, anterior view. Note homogeneous density over right upper lobe, characteristic of lobar pneumonia.

Upper right: Roentgen-ray photograph of chest, lateral view. Findings are similar to those of anterior view.

Lower left: Section through consolidated area of lung. Note exudate in alveolus, consisting of fibrin, polymorphonuclear and red blood cells and monocytes.

Lower right: Higher magnification of same section to demonstrate Friedländer bacilli in situ. Note monocyte upper left.

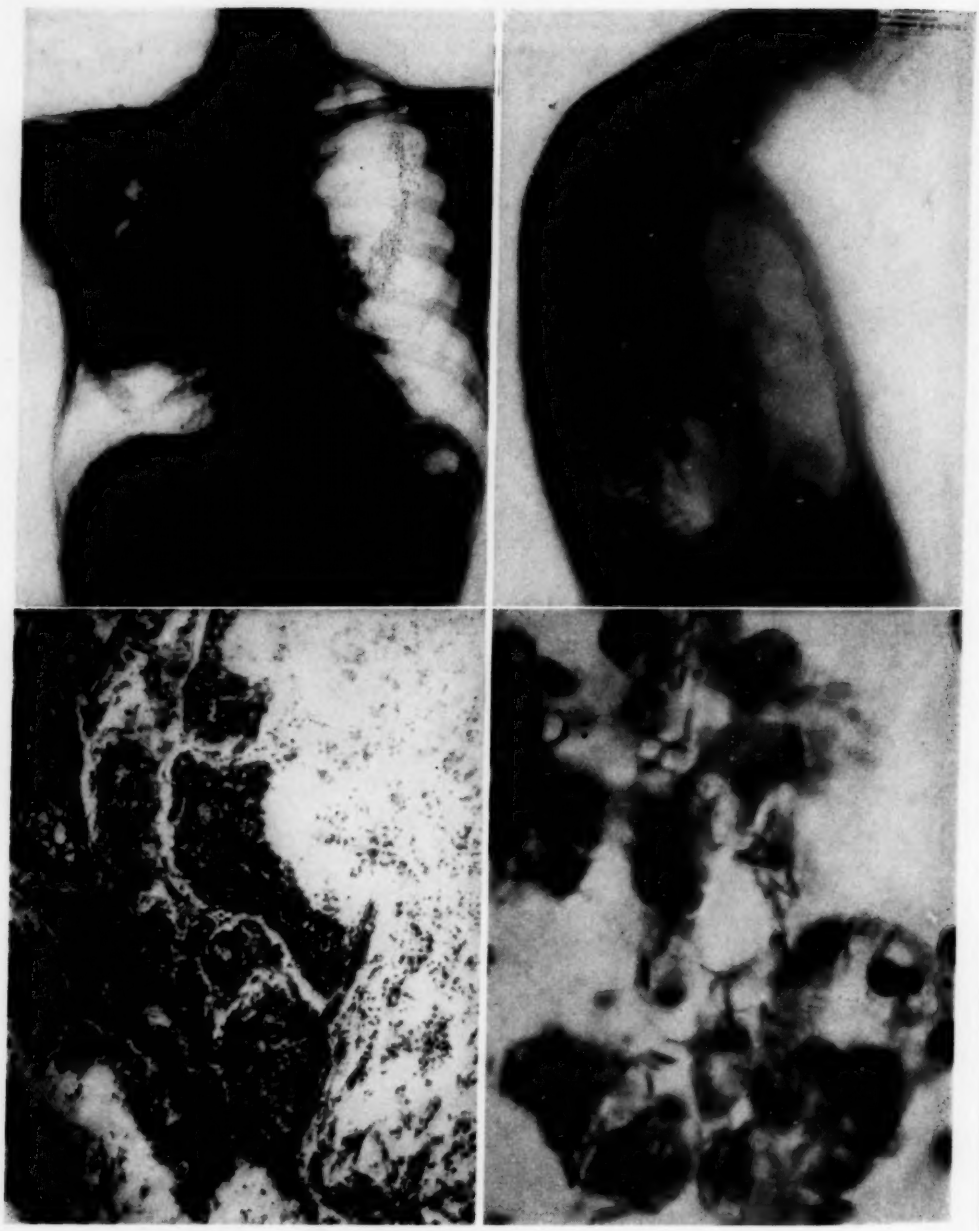

FIG. 2. Illustrations to supplement history of patient A. G.

Upper left: Roentgen-ray photograph of chest, anterior view. Note homogeneous density over right upper lobe and area of radiolucency.

Upper right: Roentgen-ray photograph of chest, lateral view. Note areas of comparative radiolucency, suggestive of cavities.

Lower left: Section through consolidated area of lung. Note particularly abscess in lower left and cavity along right with formation of wall of fibrin.

Lower right: Higher magnification of same section to demonstrate Friedländer bacilli in situ.

Types of Friedländer's Bacillus and Their Relation to Pneumonia

That there are several types of Friedländer's bacillus is now generally accepted, and there is reason for believing that Type A is by far the most frequently encountered in pneumonic disease. The detection of types is simple and three satisfactory sources are available for the purpose, of which the most commonly utilized is the sputum. Gram stains usually give the first intimation of the presence of Friedländer's bacillus, the Gram negative organism not only being in typical arrangement, but even exhibiting actual or suggestive capsules on numerous occasions. The type of the organisms may be determined from direct culture of the sputum, peritoneal washings from mice inoculated with the sputum, or preferably by the "quellung" reaction as adopted bodily from pneumococcal typing. Blood is the second source for

Table III

Incidence of the Different Immunological Types of Friedländer's Bacillus in Human Pneumonia

Types	Number of strains	Percentage incidence
A	70	64
B	15	14
C	8	7
Group X	16	15
Totals	109	100

typing, and when cultivable in such cultures, the organism may be typed directly by agglutination or by the "quellung" reaction. The third source is from the urine. Blake [39] was first to demonstrate that the urine of patients with Friedländer pneumonia may be precipitated in homologous antiserum. Later [40] this was shown to occur in the urine of animals infected experimentally. The writer has been able to determine the type of infecting organism by this method on a number of different attempts. To urine both undiluted and diluted progressively to about 1:80, is added 0.2 c.c. of antiserum and 0.3 c.c. of saline. Incubation is carried out as usual and readings are made after two hours and on the following day after standing overnight in the ice chest. The presence of precipitation in such tests indicates free polysaccharide elaborated by the infecting organism and, therefore, it designates the type of Friedländer bacilli in the lung.

Since Friedländer's bacillus may occur with other organisms also capable of causing pneumonia it becomes necessary to determine when it is primary and when secondary. Obviously in the case of positive blood cultures or of specific precipitation in the urine no other proof is needed. In typing from sputum, however, the evidence may not be so definite. While the following is not always conclusive it is nevertheless a good general rule: when pneumococci are present, the higher the number of their types the less chance of their participation in the infection. In the presence of other potentially pathogenic organisms, Types A and B are probably significant, whereas

Type C and Group X organisms are less significant. At rare times cultures are obtained by lung puncture, when the organisms usually grow in pure culture, thus rendering diagnosis reasonably certain.

Since 1926, when the types of Friedländer's bacillus were defined by immunological methods, 109 strains have been collected by the writer as involved in pneumonia, some of the strains coming from blood, others from lungs, and still others from sputa. While it may be possible that the organism in question was not always the primary infecting agent, it has nevertheless been assumed for different reasons that such was actually the case. The typings performed with these strains are summarized in table 3, where it will be seen that 70 strains or 64 per cent were Type A, 15 or 14 per cent were Type B, eight or 7 per cent were Type C, and the remaining 16 or 15 per cent

TABLE IV

Frequency of the Different Immunological Types of Friedländer's Bacillus in Fatal Pneumonia

Types	Total number of cases	Number of fatal cases	Percentage mortality
A	39	35	89
B	7	5	71
C	4	2	50
Group X	5	3	60
Totals	55	45	82

were classified as Group X. The only other typings known to the writer for comparison are those of Bullowa, Chess and Friedman [8] and Solomon.[7] The former found that of 41 patients studied, 24 or 58.5 per cent were infected with Type A organisms; whereas the latter, submitting records on only 10 patients of the 32 studied, reported that typings were conducted in seven of the 10 patients and Type A infection was established in all seven.

It may be of interest to illustrate the mortality of Friedländer's pneumonia as related to the type of infecting organism. Unfortunately it was not possible to obtain the complete records on all of the patients whose cultures were typed. Only 55 patients can be analyzed for this purpose as will be seen in table 4. Of the 55, 39 were Type A and 35 or 89 per cent died; seven were Type B and five or 71 per cent died; four were Type C and two or 50 per cent died; and finally, five were Group X, and three or 60 per cent died. Except for Type A, it is felt that the number of patients of the remaining types was too few for accurate statistics. Nevertheless, the summary reveals that 45 of the 55 patients died giving a mortality rate of 82 per cent. In this connection it should be pointed out that in Bullowa, Chess and Friedman's series 20 of 24 Type A patients died (83 per cent), two of two Type B patients died, one of one Type C survived, and six of eight Group X died (75 per cent).

Treatment of the Pneumonia of Friedländer's Bacillus

Until very recently the treatment of Friedländer pneumonia consisted almost entirely of non-specific therapy, or what is commonly designated as expectant treatment. With the evolution of types and the advent of sulfonamide drugs, it became possible to attempt specific treatment on the one

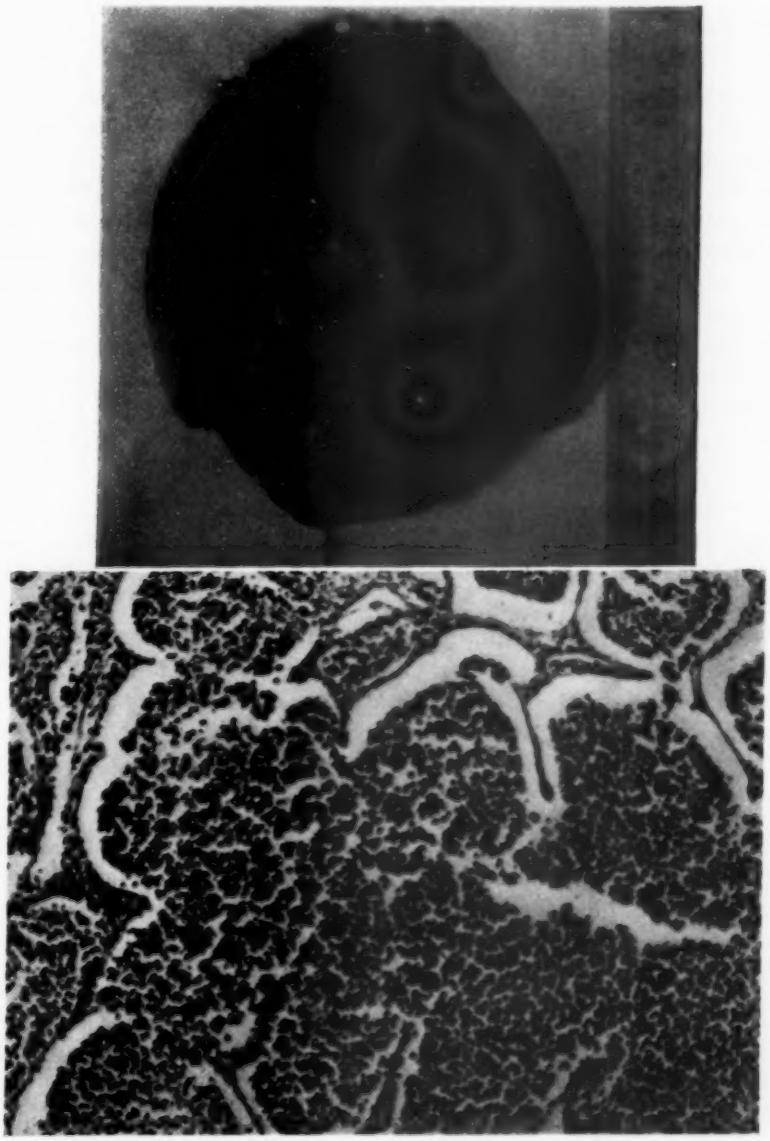

Fig. 3. Gross and microscopic changes of the lung.
Upper: Lung at post mortem, exemplifying voluminous, heavy, and consolidated appearance.
Lower: Section through infected area to illustrate large collection of polymorphonuclear cells with some monocytes, and degeneration of alveolar walls.

hand with antiserum and on the other with chemotherapy. This writer has seen three patients treated with antiserum, all suffering from fatal Type A infection. In each instance, the patients were well along in the course of the disease and did not live long enough for adequate treatment: one received 43 c.c. of serum, one 38 c.c., and the third 60 c.c. These trials obviously leave the experiment incomplete and unsatisfactory, and they are consequently of little value in appraising the therapeutic influence of antiserum. As far as can be determined, there are only two other examples of serum therapy. Solomon [7] in 1937 reported the treatment of five patients with Type A infection, all of whom died. It may be significant, however, that four of these patients died within the day the serum was given, and the fifth patient, receiving 280 c.c. of antiserum, showed a progressive septicemia and died on the third day following specific treatment, or the eighth day of the disease. It seems, therefore, that serum was not given adequate trial in this group of patients. At about the same time, Bullowa, Chess and Friedman [8] similarly experimented with serum therapy on eight patients, of whom six received homologous serum. All six patients were treated adequately, from early in the disease, and two on the seventh and sixth days of infection. Three of the patients survived and three died. Admittedly the group is small and the results are correspondingly difficult to evaluate.

Treatment with sulfonamide drugs has been observed in eight patients, six with Type A and two with Type B infection. The former were given: sulfapyridine, five patients; sulfanilamide, one patient; while the remaining two received sulfathiazole. A blood concentration of the drug was maintained at supposedly sufficiently high level (8 to 14 mg. per 100 c.c.). As far as could be determined no effect was demonstrated on the course of the infection and all eight patients died, even though the treatment was started early (within 24 to 48 hours). Undoubtedly, others must have given the drugs a similar trial (cf. patient F. G. above), even though the results of such treatment are apparently unpublished.*

Discussion

The accumulated evidence indicates quite clearly that the pneumonia of Friedländer's bacillus is a relatively uncommon disease. The same evidence, however, reveals the infection as highly fatal, holding its own in fact with the most severe bacterial diseases known to medicine. The importance of the pneumonia, therefore, resides not in its frequency, but in its mortality. The distribution of the infection among individuals of middle and old age

* Since the present communication was written, Solomon (Jr. Am. Med. Assoc., 1940, cxv, 1527–1536) has reported his observations on 17 patients with chronic pneumonia due to Friedländer's bacillus. It is interesting in this connection that four patients were treated with sulfapyridine, the pulmonary suppuration continuing and showing with little apparent effect. Another patient with bacteremia was given sulfanilamide, and while he is considered as recovered, he developed lung abscesses. It would seem, therefore, that this experience parallels that of the present writer in that the sulfonamides are of questionable value in this form of infection.

and its extreme rarity in infants and children are interesting and unexplained facts. Certainly, the infrequency of infection in young individuals does not seem to be referable to lack of exposure, if it be permissible to reason by analogy from pneumococcal pneumonia. On the contrary, it may be that in young pulmonary tissue there is some undefined property of general resistance to the organism, just as pneumococcal (lobar) pneumonia, again, is less severe in this age group than in adult life.

Although a number of similarities exist between Friedländer and pneumococcal pneumonia, the essential difference between the two forms is the tissue destruction in the former. Recovery from pneumococcal pneumonia implies a complete restoration of the involved tissue to normal, so much so in fact that no sign of the forerunning condition is detectable by roentgenological or histological examination. In Friedländer pneumonia, on the other hand, the early formation of necrosis, followed by liquefaction, cavitation, and even fibrosis, may well leave permanent testimony of past infection. In contradistinction to the pneumococcus, therefore, Friedländer's bacillus must be considered as possessing marked capacity for tissue destruction.

The high mortality in Friedländer pneumonia stresses the fact that the urgent problem in this infection is therapeutic. Obviously, general care and expectant treatment have proved themselves insufficient. Reliance at the present time appears to be on the sulfonamide compounds and on serum therapy. The results obtained with the drugs leave the writer less sanguine than does the administration of antiserum. The experiments of Bliss, Feinstone, Garrett and Long,[41] which provide the basis for drug treatment, revealed that such compounds did not bring about survival of infected mice but merely delayed death. It must be remembered, however, that prolongation of life, even for several days, is not recovery from infection. In any case, the observations cited above, while admittedly scanty, point in this direction. It is interesting to note that in a recent review of different diseases treated with sulfonamide compounds, Reimann[42] lists Friedländer pneumonia among the infections in which the drugs are of doubtful value.

The different attempts already described at serum therapy have been too few and inadequate to allow of a fair estimate of its value or potentialities. Experimental studies, however, suggest that in artificial infection at least, antiserum exhibits a considerable degree of protective effectiveness; and in vitro tests, such as agglutination, precipitation of specific carbohydrates, and "quellung" reaction, indicate an avid reactivity between antibody and capsular substance. While obviously such experiments do not assure successful treatment (cf. in this connection Type III pneumococcal pneumonia), the implication in the absence of evidence remains one of promise, as perhaps, the trials of Bullowa, Chess and Friedman[8] intimate.

Summary and Conclusions

1. The pneumonia of Friedländer's bacillus is an uncommon infection, occurring once in every hundred pneumonias.

2. The mortality of this disease runs high, attaining a rate close to 82 per cent.

3. The clinical and histological characteristics of the pneumonia are enumerated and discussed.

4. The different types of Friedländer's bacillus are found in pneumonia in the following proportions: Type A, 64 per cent, Type B, 14 per cent, Type C, 7 per cent, and Group X, 15 per cent.

5. Type A appears to be the most virulent and fatal form of Friedländer infection.

6. Possibilities of specific treatment are discussed, with the recommendation that specific antiserum be given experimental trial.

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WEIL'S DISEASE; REPORT OF THREE CASES, INCLUDING THE MORBID ANATOMY OF ONE CASE, AND A BRIEF REVIEW OF THE PERTINENT LITERATURE*

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IN 1886, H. A. Weil [1] described a syndrome characterized by the sudden onset of prostration, fever, myalgia, jaundice, hemorrhagic tendencies and renal damage which, today, is known by his name. Inada and Ido [2] discovered the spirochete in the liver of a guinea pig, inoculated with the blood of a patient suffering from the disease in 1915, and believed it to be the causative agent. They succeeded in isolating and culturing the organism and named it *Spirocheta icterohemorrhagica*. The following year Inada [3] and a group of Japanese reported extensively on the etiology and mode of infection of this disease. In 1918, Hideyo Noguchi [4] classified the organism under the genus Leptospira, as he had proposed in a previous report,[5] retaining the nomenclature icterohemorrhagica set forth by Inada.[2] Other synonyms for the disease include infectious jaundice, spirochetal jaundice, spirochetosis icterohemorrhagica, spirochetosis and recently the term leptospirosis [6] has been used to include the mild type of Weil's disease, most frequently seen in the United States.

The disease has a world-wide distribution as would be expected since the Leptospira is an ubiquitous organism.[7] However, relatively few cases have been reported in this country probably because the disease remains unrecognized in the majority of cases. In 1922, Wadsworth [8] reported the first proved case on the North American continent. Gaines and Johnson reviewed the literature on the subject and contributed seven cases from Colorado in 1937. They were able to collect 13 cases, published prior to their cases, reported from the states of New York,[10] Virginia,[11] District of Columbia,[12] Pennsylvania,[13] California [14] and Massachusetts.[15] Since 1937 we have succeeded in finding four cases reported from New York [16] and Texas,[17] making a total to date of 24 cases reported in the United States. An epidemic of this disease was the subject of a preliminary report from Detroit, Michigan [18]; and personal correspondence with the Pennsylvania State Board of Health [19] revealed four separate outbreaks of a mild type of Weil's disease in the mining areas of this state during the past year. Recent reports from all parts of the world are too numerous to include.

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In this paper we wish to report three proved cases of Weil's disease, including the morbid anatomy of one case; briefly review the subject; suggest that a method, previously described for obtaining adequate darkfield preparations from gonorrheal discharges, may be applied to routine darkfields on jaundiced patients; and discuss some of the interesting aspects of our cases as compared to other reported cases.

Case Reports

Case 1. B. F. was a married, white, Hebrew male, aged 39, resident of Philadelphia and a laborer on a W. P. A. quarry project until October 1, 1937 on which date he experienced an acute onset of chills, fever and severe prostration. The following day he noted a yellow discoloration of his skin and eyes, began to have mild nausea, epigastric discomfort, general malaise, anorexia and myalgia. During the next few days, the jaundice increased and was accompanied by generalized pruritus, his urine became dark in color and his stools acholic. The past medical and family history was negative. He was admitted to the Medical Service as an ambulatory patient October 10, 1937 and was recorded as being a well nourished, slightly icteric, middle aged male weighing 154 pounds. Slight tenderness to palpation in the epigastrium; a tender and enlarged liver whose edge extended three inches below the right costal margin and a questionably palpable spleen were the only positive physical findings on admission.

Initial laboratory studies revealed the blood Kahn, sedimentation rate, coagulation time, bleeding time, erythrocyte fragility, total erythrocytes and leukocyte counts, hemoglobin and Schilling differential to be negative or within normal limits. Abnormal findings included urine bilirubin, blood icterus index of 50, blood bilirubin 2 mg. per 100 c.c. and a qualitative Van den Bergh which gave a direct immediate reaction. A gall-bladder drainage was positive for bile pigments, negative for cholesterol crystals, contained a few erythrocytes, leukocytes and bacterial clusters in each of three specimens taken in the routine manner.

During the ensuing days of October, the patient ran a slight elevation of temperature but showed some clinical improvement. The urine became lighter, the stools darker in color. The icterus index fell to 45, the leukocyte total and differential count remained normal, but erythrocytes and hemoglobin fell gradually to 3,870,000 and 75 per cent respectively. On October 26, darkfield examination of the blood serum was positive for *Leptospira*, while a similar examination of the urine was negative.

Two days later, the patient complained for the first time of a sharp, knife-like pain across the right diaphragm, which lasted five minutes and suggested biliary colic. Following this, he continued to have epigastric distress, and on November 12 a single roentgenogram of the abdomen showed the liver and spleen to be enlarged, the edge of the liver extending down 2 cm. below the crest of the ileum, but no shadows suggesting biliary or renal calculi were noted. During the early part of November, the icterus index rose coincidentally with epigastric distress, attaining a level of 75 for the first two weeks. The urine became highly colored and the stools varied in color from dark brown to light yellow at intervals of several days. The leukocyte count rose to 11,100 with a slight shift to left in the Schilling hemogram. On November 25, the patient suffered an attack of upper abdominal pain clinically resembling biliary colic. The patient continued to have attacks of biliary colic, of increasing severity, on each of four succeeding days and the icterus index rose to 150. At this time it was felt that there was some common duct obstruction which required surgical intervention though a positive agglutination test for *Leptospira* was reported from The United States Naval Medical School on this date. On December 1, 1937, a

cholecystogastrostomy was performed through a high right rectus incision. The operative findings were recorded as follows: "Liver enlarged, spleen enlarged three times its normal size. Gall-bladder was distended with about 150 c.c. of thick, granular, dark red, hemorrhagic material which coagulated upon removal. The head of the pancreas was soft. No stones were palpated in the gall-bladder or biliary ducts." Darkfield examination of the material aspirated from the gall-bladder at operation, was positive for *Leptospira*. The patient responded well to the operation, the icterus index falling to 50, within 10 days. Operative convalescence was entirely uneventful, and during the next three months the patient appeared to be improving, though the icterus index varied between 37 and 86, averaging about 50. On March 22, 1938 daily intramuscular injections of liver extract were initiated and the patient responded shortly thereafter with a gradual rise in erythrocyte and hemoglobin values, while the icterus index progressively decreased, achieving a normal value of 6 on May 18 for the first and only time during his hospitalization. The patient felt greatly improved and clinically appeared to be well.

Early in June, a sudden unexpected and unexplainable change occurred, the patient began to fail, the erythrocytes and hemoglobin began to decline, the leukocyte count rose with increasing shift to the left, and the icterus index value gradually increased to 25. The end of June found each of these values continuing their respective rise or decline in the same direction, though there was less shift to the left in the Schilling hemogram. On July 2, 1938, the patient began to pass dark red blood by rectum and became edematous. The melena continued during the next four days, when he began to vomit blood as well. During this time, the erythrocyte count reached a level of 750,000 with hemoglobin of 10 per cent, the leukocytes rose to 27,700 and exhibited a shift to the right. The icterus index attained 75. Direct blood transfusions were given on alternate days in amounts of 500, 500, 750 and 750 c.c., but the patient failed to respond and expired July 17, 1938 following an illness lasting nine months and 17 days.

A necropsy was performed with the following gross findings: The tissues were bile stained and edematous. Both pleural cavities contained about 200 c.c. of clear, straw colored fluid, and the lungs were edematous, the right weighing 800 and the left 840 gm. The heart was slightly bile stained, the myocardium pale, and the right ventricle slightly dilated. The abdomen was filled with a greenish ascitic fluid. The gastrointestinal tract was filled with partially digested blood and the entire mucosa was covered with petechial hemorrhages. The stoma of the cholecystogastrostomy was intact and admitted one finger; the gall-bladder was filled with soft blood clots. The common duct was patent. The liver was considerably enlarged, weighing 2,775 gm., dark green in color and rather firm in consistency. On section, the surface suggested marked biliary cirrhosis. An abscess 6 cm. in diameter was discovered in the left lobe and distended both the superior and inferior surfaces; on section, it was found to be well encapsulated. Cultures from the abscess yielded *Escherichia coli*. The spleen weighed 300 gm., and appeared normal. The kidneys were pale, edematous and bile stained; the right weighed 190 gm. and the left 200 gm.

Microscopic examination of sections from the above organs revealed the following findings: The liver showed an ascending cholangitis with periductal fibrosis and infiltration of round cells about the afferent vein and biliary radicles. The bile ducts in these areas showed proliferation and budding. The liver cells varied in size and bile content; those about the afferent vein contained the most bile. The nuclei were vesicular and varied in size and number, often two or three being present in a single cell. A small amount of fatty infiltration was observed about an occasional afferent vein. Several miliary abscesses, as well as areas of focal necrosis, were noted. The latter had a central and mid-zonal distribution. What was thought to be an abscess was an extensive area of necrosis well encapsulated by fibrous tissue, and adjacent

pressure necrosis of liver cells. Extensive fibrosis in this locality was of the nodular type.

Except for an occasional group of necrotic epithelial cells, the surface of the gall-bladder mucosa was completely eroded. The surface was covered with a necrotic, hemorrhagic, fibrinous exudate which contained relatively few leukocytes. The lamina propria was swollen and tightly packed with eosinophiles and wandering phagocytes. The lower layers had undergone extensive fibrosis and hyalinization. The muscle cells showed focal degeneration, selective vacuolization and hyalinization.

The tubules of the kidneys were dilated and contained varying amounts of albumin. The tubular cells were swollen, necrotic, and occasionally contained globules of bile. The glomeruli appeared quite normal, but were often surrounded by interstitial fibrosis and edema.

The sheathed arteries of the spleen were unduly prominent. No Malpighian corpuscles persisted, but occasional minute collections of lymphocytes were noted. The entire organ was involved in a diffuse fibrosis. The sinusoids were packed with erythrocytes, round cells and hemosiderin bearing phagocytes.

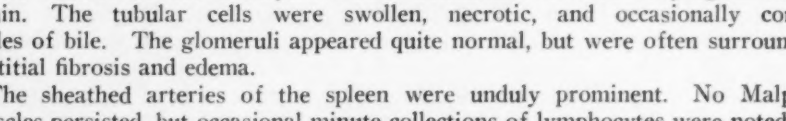

FIG. 1. Diagrammatic illustration of the area in Williamstown, New Jersey from which the rats, studied in case 2, were obtained. The garage in which the patient worked is at the left.

In the lymph nodes the stroma was very edematous, and nothing remained except a delicate reticulum in which small deep staining lymphocytes were sparsely enmeshed. No primary or secondary follicles existed. The collecting sinusoids contained considerable numbers of hemosiderin bearing phagocytes.

The pancreas exhibited slight periductal fibrosis. Several small capillary hemorrhages in the islets of Langerhans were observed.

The heart muscle was edematous and the cell striations indistinct. Occasional selective vacuolization of individual cells was noted.

The lungs were edematous and showed a terminal patchy bronchopneumonia.

The adrenals showed lipoid depletion but no evidence of hemorrhage.

Unfortunately sections from the gastrointestinal tract were not taken.

Case 2. P. W. S. was a married, white male, aged 46, who was a resident of Williamstown, New Jersey (approximately 20 miles from Philadelphia). This town had a piped water supply but no sewerage system; most dwellings and places of business used covered cesspools or outhouses. The patient worked at a garage situated in a business block with four other buildings, as shown in figure 1. Numerous rats were seen in all areas and buildings situated within the block.

For several weeks prior to the patient's illness there had been heavy rains in that vicinity and water had accumulated in the cellars of the buildings. The garage had a heater pit which the patient was required to bail out almost daily, at a time when he had several abrasions on his hands, which were in evidence on admission. He noted that the one on his thumb was especially indolent in healing.

On March 13, 1939, he experienced anorexia, weakness and malaise and the following day, had a rather sudden onset of chills, slight fever and moderate prostration. Two days later his skin became yellow and his urine dark in color. During the next few days his symptoms abated but, on March 20, the fever and prostration returned, the jaundice increased, the urine remained dark and his stools became clay colored. He developed a marked pruritus which caused him to scratch himself. These scratches bled freely and purple lumps raised up about the abrasions. Again the fever, prostration and other symptoms receded though the jaundice remained the same. He was admitted as an ambulatory patient to the Medical Service on March 24, 1939. On admission, he had a temperature of 99° F., the skin and sclerae were moderately icteric and there were multiple scratch marks over the whole body with peculiar secondary inflammatory purple areolae about some of the lesions. The left lobe of the liver was barely palpable and not tender. The spleen was not palpable. There were no other positive findings.

Initial laboratory studies included the darkfield examination of the blood serum which was positive for *Leptospira*. The icterus index was 35, the qualitative Van den Bergh biphasic, urine was positive for urobilin but darkfield negative. The total erythrocyte and leukocyte counts, hemoglobin, Schilling hemogram, erythrocyte fragility test, coagulation and bleeding time were within normal limits. Guinea pig inoculations were made with the patient's blood and with catheterized urine. A specimen of blood was sent to the United States Naval Medical School for agglutination tests. The patient was placed on a high carbohydrate, high vitamin, dietary regime and was allowed to be active about the ward. At no time after admission did his temperature go above 100° F., he felt well and complained only of pruritus. Repeated darkfields on the urine were negative, but a positive result was finally obtained on April 4. The icterus index gradually receded to 6 by April 20, reaching 3 on April 26, rising again to 12 without any new symptoms and finally receding to normal at the time of discharge. The hemorrhagic inflammatory lesions gradually healed. Darkfields on serum from these lesions were negative. Darkfields on blood and urine on May 17 were both negative and the patient was discharged completely well. A follow-up since that time found the man in good health.

The agglutination test taken on March 27 proved to be negative against the strain of *Leptospira* used at the Naval Medical School.

Both the inoculated guinea pigs appeared to be ill on the eighth day and died on the tenth day following the injections. No jaundice was noted in either pig. However, they were light tan in color and it may have been overlooked.

Autopsy findings on the blood injected pig revealed a subcutaneous hemorrhage in the abdominal wall, the lungs were slightly hemorrhagic and there were two extravasations of blood into the superficial cortex of the right kidney. The liver was not grossly abnormal, the gall-bladder was distended with lemon yellow bile. Darkfield examination of the blood serum was positive, but the urine and bile were negative.

Autopsy examination of the urine inoculated pig disclosed "butterfly type" hemorrhages in the lungs, and the gall-bladder was distended with hemorrhagic bile. The liver, spleen and kidneys were not grossly abnormal. Darkfields on the urine were negative. Darkfields on the bile showed an occasional *Leptospira* and those on the blood serum contained 2 to 3 organisms per oil-immersion field. A Fontana stain of the pig's blood serum showed *Leptospira*.

On March 29, 1939, a rat was brought in from the colony about the garage. It had been caught in a trap and had been dead 48 hours. Postmortem examination

showed pulmonary hemorrhages, a yellow, speckled liver, and engorged kidneys. Darkfield examination of a liver emulsion was negative for *Leptospira*. Sections of the lungs, liver and kidneys were made and were stained by Levaditi's method. The cells of the renal tubules contained an occasional *Leptospira*.

On April 17, 1939, a live rat from the colony at Williamstown was obtained. The rat was anesthetized with ethyl chloride, a piece of its tail was cut off, and darkfield preparations were made from the blood. Examination of the preparations showed numerous *Leptospira* which resembled those seen in the patient's blood and in that of the guinea pig. Preparations were being made to make further studies of the rat on the following day. The rat survived the anesthesia and appeared well immediately after the darkfield preparations had been made, but it died that night and was not discovered for some time. Darkfields on the blood, urine and liver emulsions of the dead rat were negative.

Case 3. M. O. was a healthy, single, dark complexioned white female, aged 19, who was studying art in Philadelphia. She resided in the southern part of the city, where large vacant fields, formerly used as piggeries, surrounded her dwelling place. On several occasions she had seen rats in the kitchen and dining room, but denied direct contact with them. She did recall releasing a mouse from a trap some time prior to her illness and admitted nocturnal barefoot excursions to the kitchen.

On March 19, 1939, she developed anorexia, malaise, moderate prostration, slight chills and fever, which continued for several days. On the fourth day, she began to have a dull pain and tenderness to palpation in the right upper quadrant. These symptoms became more marked. She developed a generalized pruritus and, on March 26, it was noted that her sclerae were yellow. During the next few days, the fever, malaise and prostration abated, but the jaundice increased, an icterus index reading on March 27 being 12. On April 1, the skin was definitely icteric, and she continued to have occasional attacks of right upper quadrant pain. A blood count showed 4,150,000 erythrocytes, 78 per cent hemoglobin and 5,300 leukocytes with a differential of 44 per cent neutrophiles of which 36 were segmented and 8 were band forms, 45 per cent lymphocytes and 11 per cent monocytes. The blood sedimentation rate was 15 mm. in 60 minutes.

Her urine became very dark and the stools clay colored. She remained ambulatory, but had a return of anorexia and malaise as the jaundice deepened. On April 4, the icterus index was 28, the qualitative Van den Bergh gave a positive biphasic reaction, and the Takata test was positive. A darkfield examination of the blood serum on April 8, disclosed *Leptospira,* while a similar examination of the urine on April 10, was negative. The urine was strongly positive for bilirubin but was otherwise negative. A gall-bladder drainage, on April 17, 1939, contained a small amount of bile pigment and a few erythrocytes, leukocytes and epithelial cells in each of the three routine samples. The icterus index continued to rise and was 75 on April 19. On April 23, she began to run a low grade fever, had nausea, indigestion and a rather irritating cough. She had lost 12 pounds since the beginning of her illness. On April 26, she was admitted to the Medical Service, where physical examination revealed marked jaundice of the skin, sclerae and mucous membranes as the only positive findings. The liver and spleen were not palpable.

The icterus index attained a value of 150 for two readings over a period of seven days, during which time the patient became almost psychotic from the intolerable pruritus and the continual bronchial irritation and cough. On April 4, intramuscular injections of liver extract were initiated, and the patient responded with immediate clinical improvement, the icterus index falling to 100 on April 6 and to 30 on April 9. The cough and pruritus receded with the jaundice and she was discharged on April 20, 1939 convalescent, a follow-up showing complete recovery with a recent normal liver function test.

While under study, this patient had a doubtful positive blood Kahn test, although there is no reason to suspect the possibility of luetic infection.

On April 12, two guinea pigs were inoculated with whole blood and with catheterized urine, obtained from the patient under sterile precautions. Both pigs appeared to be ill on the seventh day. The blood inoculated pig died on the eighth day and the urine inoculated pig died on the tenth day. Both pigs showed typical postmortem changes, with butterfly hemorrhages over the base of the lungs, hemorrhagic bile and congestion of the liver and kidneys. Darkfields on the blood of both guinea pigs were positive for *Leptospira*.

Bacteriology, Epidemiology and Immunology

The *Leptospira* are a genus of spirochetes, so named because of their fine coils, to quote Noguchi's original description:[4] "the number of coils is greater in a given length than that of any spirochete hitherto known." Their length is variable from 3 to 40 mu, averaging about 9 mu. One or more gentle undulations occur throughout the entire length. The ends are sharp, and one or both may be semi-circularly hooked or formed as an eyelet. Most characteristic is the highly motile end portion consisting of the last 6 to 8 spirals which seem to flex on the organism. Upon darkfield examination, one or both ends appear club-shaped, and the tightly wound coils may appear as chains of coccoid bodies. This spirochete is quite active and usually takes an erratic course, with rotation and lashing movements of the extremities. The organism may be stained by either Levaditi's or Fontana's method. In these preparations the *Leptospira* appear much thicker because of the deposition of silver salts upon their surface. Readers who are unfamiliar with the identification of these organisms are referred to the reports of Inada[3] and Noguchi[4] which include numerous microphotographs of darkfield and stained preparations.

In the course of our investigations on cases 2 and 3, we found the method described by Friedman,[20] for obtaining darkfield preparations of *Treponema pallida* from gonorrheal discharges, highly advantageous and satisfactory, especially for obtaining blood serum from the dead guinea pigs. Briefly, the technic consists of obtaining the specimen in a section of ordinary capillary glass tubing approximately 10 cm. in length, such as that used in routine coagulation tests. After the specimen has been obtained, the opposite end from which the specimen was taken is sealed in a Bunsen burner. The capillary tube is then placed, sealed end downward, in a centrifuge tube and is centrifuged for 5 to 10 minutes. It is then removed and it will be found that the sealed end contains the cellular portion of the specimen. This is broken off just to the serum side of the line demarcating the clear supernatant fluid from the cellular suspension. A bulb from a smallpox vaccination set is placed on the end of the capillary tube, and the clear, supernatant fluid or serum is expressed upon a cover slip, which is then set up in a routine manner. This technic was used in the study of the patients, by taking the capillary

specimen from oxalated blood drawn for blood chemistry or for the sedimentation rate. In these preparations we found more *Leptospira* per field than with any other method when both preparations were taken from the same specimen at the same time. We recommend this method for routine darkfield examinations on all jaundiced patients.

Authorities vary as to the difficulty of obtaining cultures of these organisms. The non-pathogenic *Leptospira biflexa* may be cultured on autoclaved suspensions of feces, to which 5 per cent nutrient agar or gelatin may be added.[7] Noguchi [4] recommended a medium consisting of rabbit serum one part; normal saline or Ringer's solution, three parts; and 0.5 part rabbit plasma, covered with a thin layer of sterile paraffin oil, for the growth of *Leptospira icterohemorrhagica.* We were unable to obtain positive cultures from our cases on the ordinary blood and ascitic media.

Weil's disease is evidently contracted by infection of the intact or abraded skin from contaminated water.[3] A group of Japanese workers [21] also noted that the disease was common in wet mines in which the workers went barefoot, that it was endemic in regions with neutral or alkaline soil; but was rare or absent in dry mines or regions in which the soil was acid. The water is believed to be contaminated by the urine of wild rats which are frequently found to be infected with *Leptospira icterohemorrhagica* (Blumer). Wild mice are not generally infected since their habitats are not so closely associated with water, but they may transmit the disease.

In California, cases were traced to the handling of dogs suffering from "yellow or Stuttgart's disease." A survey of dogs suffering from the disease showed them to be infected with either *Leptospira canicola* or *Leptospira icterohemorrhagica.*[6] The disease caused by the former strain of *Leptospira* has been called Canicola fever, runs a much milder course, and is often without jaundice. The transmission of Weil's disease by dogs is an accepted fact, having been proved in several cases. Numerous epidemics and cases have been traced to bathing in swimming pools, ponds or lakes. Jeghers, Houghton and Foley [15] ridicule the possibility of human carriers, but we feel that this is a definite means of contamination.

Infection with Weil's disease confers a definite and lasting immunity which appears to be humoral in character. The antibodies which develop resemble those of a syphilitic infection to some extent since the Wassermann reaction may become positive during an attack of infectious jaundice.[22] As criteria of infection, serological tests are not reliable because of the antigenic variation of the many strains of *Leptospira.* Antibodies have been demonstrated in the blood as early as the fifth day, but they reach their maximum development about the twenty-fifth day of the disease. With their development, the spirochetes disappear from the blood and are found in the urine on the sixth or seventh day, persisting there as long as 40 to 60 days, reaching a peak at about 25 days.

Pathology

The morbid anatomy is mainly concerned with the effect of jaundice and capillary damage upon the various organs of the body. After a study of the pathology of this disease, Dawson, Hume, and Bedson [23] report that the principal changes are confined to the abdomen, especially the gastrointestinal tract, liver, kidney and biliary tract.

Any part or the entire gastrointestinal tract may be found peppered with petechial hemorrhages under the mucosal or serosal surfaces. Large hemorrhages into the wall of the intestines may occur and most commonly involve the duodenum. The duodenum shows a definite inflammatory reaction,[24] usually most marked about the ampulla of Vater. This affects that portion of the ductus choledochus within the duodenal wall, and it may become obstructed due to the edema and swelling, secondary to the inflammation.

The liver is usually slightly enlarged and bile stained,[25] but otherwise is grossly normal. It is never shrunken as in acute yellow atrophy. Microscopically, evidence of biliary stasis is found about the central portion of the lobules. Round cell infiltrations are scattered through the organ. The nuclei of the liver cells are swollen and often number two or three in a single cell. Bates [26] observed both focal and widespread necrosis of the liver parenchyma. Numerous other observations have been recorded but these are not significant.

The kidneys are usually slightly swollen, bile stained and frequently have subcapsular hemorrhages of varying size. In the majority of cases, the microscopic findings are confined to the tubules, though various degrees of focal and diffuse glomerulonephritis have been reported. The cells composing the tubules are swollen and necrotic. Various degrees of interstitial fibrosis and lymphocytic infiltration occur, and small capillary hemorrhages are quite characteristic.

The skeletal muscles, and more rarely cardiac muscle, show varying amounts and degrees of punctate hemorrhages, focal degeneration, loss of striations, and selective vacuolization of individual muscle fibers. Round cell infiltrations are commonly seen. A peculiar type of hyalinization [15] of the muscle bundles, comparable though not resembling Zenker's hyaline degeneration as seen in typhoid fever, is considered quite characteristic of this disease.

The spleen is usually not enlarged. Heavy deposition of hemosiderin and numerous monocytes containing phagocytosed erythrocytes are the most common microscopic findings.

Two cases terminating in acute hemorrhagic pancreatitis [27] have been reported. Various pathologic changes in the skin, lungs, adrenals and other organs are described, but these simply reflect the effect of capillary damage and jaundice in the respective organ.

Clinical Picture

Inada [3] defined three stages in the appearance of the clinical manifestations of this disease. A febrile or first stage, second, the icteric and hemorrhagic stage, and finally the convalescent or third stage. A description of the classical symptoms will be offered but the cases reported from the United States have rarely conformed to these definite divisions and have presented a much less acute picture.

Table I

	Symptoms and clinical findings												Demonstration of *Leptospira* by darkfield			Demonstration of stained *Leptospira* in sections or smears	Demonstration of *Leptospira* by guinea-pig inoculation				Final outcome
	Initial chill	Fever	Prostration	Jaundice	G. I. complaints	Nervous symptoms	Myalgia	Conjunctivitis	Hemorrhagic diathesis	Hepatomegaly	Splenomegaly	Leukocytosis	Blood	Urine	Bile		Blood	Urine	Cerebro-spinal fluid	Macerated tissue	
1.	N	P	P	P	P	–	–	–	–	–	–	P	P	–	–	–	P	–	–	–	R
2.	–	P	P	P	P	P	P	–	P	–	–	–	–	–	–	P	–	–	–	–	D
3.	P	P	P	P	–	–	P	N	–	N	N	–	P	–	–	–	–	–	–	–	R
4.	–	P	P	P	–	P	P	N	P	P	N	N	–	–	–	–	N	P	–	–	R
5.	P	P	P	P	P	P	P	P	P	P	N	P	–	–	–	P	–	–	–	–	D
6.	P	P	P	P	P	P	P	N	P	P	N	P	P	–	–	–	P	–	–	–	D
7.	P	P	P	P	P	P	P	–	P	P	N	P	N	N	–	–	P	N	–	–	R
8.	P	P	P	P	P	P	P	–	P	P	N	P	–	–	–	–	N	P	–	–	R
9.	P	P	P	P	P	P	–	N	–	P	P	P	–	–	–	–	N	P	P	–	R
10.	N	P	P	P	P	P	P	N	N	P	N	P	N	N	–	–	P	N	–	–	R
11.	–	P	P	P	P	P	–	–	–	P	N	P	–	–	–	P	N	N	–	–	D
12.	P	P	P	P	P	P	P	P	P	P	N	P	–	–	–	P	–	–	–	–	D
13.	P	P	P	P	P	–	–	–	P	N	N	N	–	–	–	P	N	N	–	P	D
14.	N	P	P	P	P	P	N	N	P	N	N	N	P	N	–	–	N	P	–	–	R
15.	N	P	P	P	P	N	P	P	P	P	N	N	P	N	–	P	N	P	–	–	D
16.	N	N	P	P	P	P	N	N	N	N	N	N	P	N	–	–	P	N	–	–	R
17.	N	N	P	P	P	P	P	N	N	N	N	N	P	N	–	–	P	N	–	–	R
18.	N	N	P	P	P	P	P	N	P	N	N	N	P	N	–	N	–	–	–	–	D
19.	N	P	P	P	P	P	N	N	P	N	N	N	P	N	–	–	–	–	–	–	R
20.	N	N	P	P	P	P	N	N	P	N	N	N	P	N	–	–	–	–	–	–	R
21.	P	P	P	P	P	–	P	–	P	P	N	P	N	N	–	P	N	P	–	–	D
22.	P	P	P	P	P	P	P	–	–	P	P	–	–	–	–	–	–	–	–	–	R
23.	P	P	P	P	P	P	P	–	–	P	P	–	P	–	–	–	–	–	–	–	R
24.	–	P	P	P	–	–	P	–	P	P	P	–	N	P	–	–	–	–	–	–	D
25.	P	P	P	P	P	N	P	N	P	P	P	P	P	N	P	–	–	–	–	–	D
26.	P	P	P	P	N	P	N	N	P	P	N	N	P	P	–	P	P	P	–	–	R
27.	N	P	P	P	P	P	N	N	N	N	N	N	P	N	–	P	P	P	–	–	R

Code: P = Present, palpable, or positive. N = Not present, not palpable or negative. – = Not mentioned or not performed. R = Recovery. D = Death.

Febrile Stage. After an incubation period of about one week the febrile stage is ushered in with the abrupt onset of chills, fever and severe prostration. These are followed by gastrointestinal disturbances and abdominal pain, nausea and epigastric colic being the most prominent of these symptoms. Headache and myalgia are frequent complaints. Occasionally, there is a cough, various cutaneous manifestations, and conjunctivitis; the latter being

considered a characteristic and important manifestation by numerous writers. This stage lasts seven to eight days, the above symptoms gradually becoming less severe as the second stage is approached.

TABLE II

		%
Positive Symptoms and Clinical Findings	Jaundice	100
	Prostration	100
	Fever	85
	G. I. Complaints	85
	Nervous Symptoms	74
	Hemorrhagic Diathesis	63
	Myalgia	63
	Hepatomegaly	59
	Initial Chill	48
	Splenomegaly	18
	Conjunctival Congestion	11
Positive Diagnostic Procedures	Darkfield Blood	52
	Stained Sections	33
	Guinea Pig Inoculation Urine	29
	Guinea Pig Inoculation Blood	25
	Darkfield Urine	7
	Guinea Pig Inoculation Mac. Tissue	7
	Darkfield Bile	3
	Guinea Pig Inoculation C-S Fluid	3
	Mortality	40

Icteric or Toxic Stage. Jaundice gradually appears in about 50 per cent of the cases, though it was reported in all of the American cases (see tables 1 and 2). A hemorrhagic diathesis occurs in a majority of cases, being more severe when icterus is present. It may manifest itself in the skin, conjunctiva, gums, or mucous membranes of the gastrointestinal and renal tracts. Marked weakness and nervous symptoms accompany the above manifestations. The liver becomes palpable and tender. Splenomegaly is absent in a majority of cases and is considered not characteristic of this disease. It is during this stage that death most frequently occurs if the case is destined to terminate unfavorably.

Convalescent Stage. This stage begins about the third week and is characterized by the regression of all symptoms and the gradual diminution in the intensity of the jaundice. An after fever is seen in some cases and this may last from four days to three weeks. Inada [3] believes this fever is caused by the disintegrating toxins during the height of the serologic immunity.

Attention is again called to the fact that the American cases have been mild, 10 to 20 per cent remaining ambulatory throughout the course of the disease. A more practical description of the stages of this disease, based on laboratory findings, as related to clinical symptoms, has been proposed.[15] This allows a more labile concept in the time of appearance, duration and severity of the symptoms. The first stage is characterized by the free circulation of *Leptospira*, by absence of humoral antibodies from the peripheral blood and by a lack of spirochetes in the urine. With the beginning of the

second stage, the number of *Leptospira* in the blood diminish and they begin to appear in the urine, while the antibodies increase in titer. During the third stage, the *Leptospira* in the urine are abundant at first after which they gradually diminish, but they cannot be found in the blood stream where well developed antibodies are now present. This conception of the disease explains many of the discrepancies in the appearance and duration of signs and symptoms reported in the American cases.

Clinical Laboratory Procedures

I. Darkfield examination of blood, urine and bile.

It is recommended that the blood and urine be examined according to the stage of the disease. Most authors claim that the *Leptospira* disappear from the blood on the ninth day, but this does not appear to be exactly true, since the organisms in the blood have been demonstrated as late as the sixty-first day.[9] On the tenth day, they begin to appear in the urine, persisting there as long as 60 days. The demonstration of spirochetes in urine seems to be much more difficult than in blood. We were able to find the organism in the bile. A method for obtaining adequate darkfield preparations was described earlier in this paper.

II. Guinea pig inoculation.

This is the usual and most satisfactory method of establishing the diagnosis of infectious jaundice. Five c.c. of whole blood, or spinal fluid, or 10 c.c. of freshly catheterized urine are injected intraperitoneally into guinea pigs. After an incubation period of five or six days the pigs become ill and heavily jaundiced. The animals die in from seven to ten days in most positive tests.

Guinea pigs may become ill but may fail to succumb to the disease; under these circumstances, they should be killed and examined on the tenth day.[10b]

Postmortem examination reveals jaundice of the skin and other tissues; petechial hemorrhages into the skin and muscles of the abdomen, beneath the peritoneum and in the gastrointestinal mucosa; most characteristic are the hemorrhages over the surface of the lower lobes of the lung, which are spotted in appearance and suggest the wing of a mottled butterfly.[23] Acute congestion of and hemorrhages into the kidneys and adrenals are frequently encountered. *Leptospira* may be demonstrated in darkfield preparations of serum and liver emulsions. They may also be found in tissue sections of the liver and kidneys stained by Levaditi's method.

III. Pfeiffer phenomena and immune guinea pig inoculation.

This method consists of mixing the blood or urine to be injected with an equal amount of anti-serum. The mixture is then incubated at 37° C. for one hour, after which it is injected intra-peritoneally as above. After one hour, repeated examination of the peritoneal fluid obtained by sterile capillary tubes will fail to show *Leptospira* while they may be demonstrated in the control animals which were inoculated without anti-serum.

The adequately protected pigs survive more than 12 days but may die later, from the fourteenth to the nineteenth day,[28] while the unprotected controls die in from the five to twelve days with the usual postmortem findings.

IV. Blood culture.

Culture of the patient's blood has been successful in the hands of some investigators. Manteufel[29] added 2 to 3 c.c. of blood to each of several sterile tubes containing 3 to 10 c.c. of sterile, distilled water. The tubes were then incubated three to four days at 25 to 30° C., and he found that at least one of the dilutions would show the organisms by darkfield examination. The *Leptospira* will live in this medium for three to four weeks.

V. Agglutination tests.

These should be attempted after the tenth day of the disease. A titer of 1/100 is significant at this time. During the next four to six days, it rises rapidly to 1/1000, after which the titer may attain a maximum of 1/10,000 to 1/50,000 about the twenty-fifth day. In acute cases, failure of the titer to rise above 1/300 should cause suspicion as to the real identity of the disease in question. Following the convalescent period, the titer gradually decreases and by the end of the first year reaches a value of 1/300, where it remains rather constant for many years, if not throughout life. This test is of great value in diagnostic surveys of cases suspected of previous infection. It is not entirely reliable in the acute cases because of the persistent antibodies in previously recovered cases and because of the antigenic variation in the strains of *Leptospira*.

The complement fixation test has been used with marked success by Gaehtgens[30] who found equally good positive results when compared with the agglutination tests. He claimed that the negative reactions were more clear cut with his method since the agglutination test with the lower dilutions is often questionable.

Recently, a precipitation test[31] and an adhesion test[32] have been described. Advocates of the latter test say that it is more rapidly performed and more easily read than the tests now in general use. As yet, none of the serological tests is available to all clinics; so most clinicians must rely on darkfield examination and guinea pig inoculations.

Treatment

A therapeutic serum is readily obtained by the immunization of horses or rabbits with cultures of *Leptospira icterohemorrhagica*. The serum is effective in man up to the fifth or sixth day of the disease, when injected intravenously in doses up to 60 c.c. in 24 hours. Most workers[21] agree that the serum lessens the severity of the disease by reducing the duration of the jaundice and the extent of the hemorrhages. Others claim that the serum causes the blood to become free of spirochetes in a few days.

Reports as to the efficacy of convalescent serum vary, good results being obtained from sera which contain a high agglutinating and lytic titer.

Gaines and Johnson [9] treated four patients with serum from recently recovered cases with good results. Either type of serum is indicated, if available, but is definitely of limited value.

Arsenicals have proved to be of no value in the therapy of Weil's disease.[15] They have been shown to be ineffective as Lepto-spirocheticidal agents, though neoarsphenamine will cause the organisms to disappear from the blood.[21] The use of these drugs carries the added danger of further injury to an already damaged liver.

Bismuth Yatren A, a soluble preparation of bismuth, has been used with success on experimental animals but, as yet, has not been used on man.[7]

Symptomatic treatment is, of course, a necessity. A high carbohydrate, low fat, high vitamin diet is recommended. We found considerable symptomatic improvement in several cases following the daily injection of massive doses of liver extract.

Prophylaxis

Prevention of the disease is most readily achieved by improvement of hygienic conditions in endemic districts, control of rats, disinfection or drainage of soil and water being of primary importance. Individual precautions include suitable protection against skin infection. Wani, Inada and Baerman, independently used methods of vaccination to establish active immunity in endemic districts and strikingly lowered the incidence in many instances. Active immunity on a large scale is not practicable but is recommended for use in certain groups constantly exposed to the infection.

Discussion of Reported Cases

In each of our cases the infection was definitely associated with rats. In case 2 we were able to demonstrate *Leptospira* in a living and dead rat from the immediate vicinity in which the disease had been contracted. So far as we have been able to determine, no other previously reported American case has been traced directly to the source. Case 1 was a W. P. A. worker employed on a project in an old quarry, as were both cases reported by Mulholland and Bray.[11, 16]

In all the cases the disease had an acute onset which caused the patients to go to bed for several days, during which time the acute symptoms gradually subsided as the jaundice became manifest. Chills, fever or prostration heralded the onset of the disease in each case. These initial symptoms were found in the majority of the American cases. (Tables 1 and 2.) On admission, each of the patients was ambulatory and mentioned jaundice and pruritus as their chief complaints. The jaundice appeared from two to seven days after the onset and, during the course of the illness increased to a peak within two weeks, receded slightly, and then increased to a second peak somewhat higher than the first, gradually disappearing thereafter. In case 3 the

jaundice reappeared during the terminal phase of his illness. Though much has been written concerning Leptospirosis without jaundice, every case so far reported in the United States has had icterus.

From the patient's point of view in each of our cases, pruritus accompanying the jaundice was the most disturbing symptom. In case 3 the itching was so severe that the patient almost became psychotic. This symptom appeared to be the direct cause of the patient's nervous manifestations. In case 2 pruritus was the primary cause of the only hemorrhagic lesions seen in this patient. Other reports fail to mention this symptom or merely include it among the unimportant symptoms. Control of pruritus will control the nervous symptoms in a majority of cases.

A hemorrhagic diathesis appeared in case 1 nine months after the patient had acquired the infection and this seemed to be directly responsible for the patient's demise. These hemorrhages were traced to the gall-bladder mucosa, although the entire gastrointestinal tract was peppered with petechial hemorrhages.

Gastrointestinal complaints occur in 85 per cent of the reported cases. In case 3 these were limited to mild epigastric pain and nausea, but in case 1 these symptoms occurred during the first few weeks of the illness, disappeared for several weeks and reappeared as a typical, severe, biliary colic from the fifty-fifth to the sixtieth day, at which time it was believed that the patient had a complete obstruction of the bile duct. At operation, no stones or other lesions were demonstrated, but a cholecystogastrostomy was performed, after which his acute symptoms subsided. This has been observed in several other American cases in which the patients were operated on, one requiring a choledochoduodenostomy.[9] Evidently, these patients had an intramural, inflammatory process upon the posterior wall of the duodenum, which could not be demonstrated by an anterior approach. Similar lesions have been described by Dawson and others.

Myalgia was a prominent complaint, occurring in 65 per cent of the other cases but was seen only in case 1 and this was very mild.

Case 3 presented a severe, persistent cough toward the end of the second stage at the height of the icterus. It was a most distressing symptom and prevented the patient from obtaining any rest. There was some speculation as to the exact cause of this symptom, some believing it to be due to *Leptospira* in the bronchi, while others attributed this manifestation to jaundice of the mucous membrane comparable to the pruritus which accompanies icterus of the skin.

Each patient noted, early in the disease, that his or her urine was dark and the stools clay colored. Bile pigments appeared in the stools in amounts indirectly proportional to the rise and fall of the icterus index values.

Enlargement of the liver occurred in both male patients, but was absent in the female. Case 1 exhibited the greatest enlargement which extended below the crest of the ilium and was associated with splenomegaly.

We were able to demonstrate *Leptospira* in the blood of each patient by darkfield examination and little difficulty was encountered. A method facilitating this procedure has been described. All the cases exhibited organisms in the blood after the ninth day, which is contrary to the findings of Inada and others. They were noted on the twenty-sixth, eleventh and nineteenth days of the respective illnesses. In the urine the *Leptospira* were more difficult to find and they were seen only in the second case on the twenty-second day of the disease. In case 1 the contents aspirated from the gall-bladder at operation contained *Leptospira* which were demonstrated by darkfield examination on the sixty-first day of the disease. Among the cases reported in the United States, this is the first case in which *Leptospira* have been demonstrated in the bile.

Though the possibility of human carriers has been doubted,[15] we feel it is a real danger since *Leptospira icterohemorrhagica* have been demonstrated in human feces and urine by Frugoni and Cappellani,[33] and many cases have been contracted in swimming pools which are well known to be contaminated from human sources. In case 1 the terminal pathology centered about the biliary tract which may have been a reservoir of infection.

Cases 2 and 3 were proved by guinea pig inoculations of the blood and urine on the fourteenth and twenty-fourth days, respectively. All four pigs died with typical necropsy findings, and *Leptospira* were demonstrated by darkfield in each animal.

In the American cases the organisms have been demonstrated in the blood by various methods after the ninth day of the disease, persisting as long as 63 days.[9] From the present concept that *Leptospira* disappear from the blood as immune bodies appear, variation of the length of time that the organisms are found in the blood is to be expected, since it is well known that some individuals develop immunity more or less rapidly than others, and vary as to the maximum immunity attained. From these observations, the finding of *Leptospira* in the blood after the ninth day is not unusual. Most clinicians report difficulty in the demonstration of *Leptospira* in the urine by darkfield, although textbooks would lead one to believe that this is a simple procedure. Guinea pig inoculations of urine give much more satisfactory results.

In all cases the leukocyte count showed little variation which could be attributed to the disease per se, and this is substantiated in 50 per cent of the reported cases. The qualitative Van den Bergh test gave a direct, immediate reaction in case 1 while the reaction was biphasic in the other two. It would appear that this test merely reflected the amount of jaundice present in each case since it was direct during the periods of heavy jaundice. This is substantiated in other types of icterus.

It is interesting to note that the case in which a luetic infection could be least suspected had the only false positive Kahn reaction, as has been described by Manteufel.[29] This case is the third female to be reported in the

United States out of 27 reported cases. The marked difference in incidence is attributed to fewer occupational hazards.

In case 1 the necropsy findings were quite typical of the pathology described by others, including the finding of extensive liver necrosis as reported by Bates.[26] The pathologic picture in this case reflects the duration and severity of the man's illness.

That this liver necrosis might have resulted in a primary hepatic failure in the formation of prothrombin was suggested by Dr. Albert M. Snell of Rochester, Minnesota. Under such circumstances, the hemorrhagic tendency might easily be explained upon prothrombin deficiency. Unfortunately, studies of this nature were not pursued, but it is suggested that all cases should be studied thoroughly from this angle.

Massive doses of liver extract were found to be of great value in the symptomatic therapy of this disease. The initiation of these injections was followed by a decrease in the icterus index values, which may, however, have been purely coincidental.

The general mortality from infectious jaundice thus far reported in the United States is 40 per cent, and our figure approximates this.

Summary

Weil's disease is endemic in the United States and should be given consideration in the differential diagnosis of all icteric cases. In general, our cases resembled the cases previously described in this country. The acute onset of chills, fever and prostration which gradually diminish as jaundice and epigastric distress appear, should be a leading point in the consideration of this disease as a possible diagnosis. The majority of the American cases are indirectly associated with a history of rat contacts. We have traced one case directly to a colony of rats in New Jersey.

The application of a previously described method for obtaining adequate darkfield preparations has been suggested as a routine examination of all jaundiced patients. The persistence of *Leptospira icterohemorrhagica* in the blood after the ninth day of the disease has been definitely established in previous reports, as well as in our cases. The length of time that these organisms persist in the blood depends on the immunological response of each individual patient. We believe we have reported the finding of *Leptospira* in the bile for the first time in the American literature and suggest the possibility that the gall-bladder may act as a focus of infection and that the patient may become a human asymptomatic carrier of the disease. Demonstration of the *Leptospira* in the blood or urine by positive guinea pig inoculation is adequate proof of the disease. The agglutination test is not reliable but is of confirmatory value.

The possibility that prothrombin deficiency may play a rôle in some of the hemorrhagic manifestations of this disease has been suggested. To date, no studies have been reported on this subject.

Liver extract is of great value in the symptomatic therapy of this disease.

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THERAPEUTIC STUDIES IN HYPERTHYROIDISM *

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For several years attempts to suppress hyperthyroidism by various medicaments have been carried out in our clinic. The rationale of this project is furnished by the occurrence of spontaneous remissions occasionally observed in this disease and the physiological demonstration of a chalone type of mechanism in other endocrine relationships. Of the latter, pituitary suppression by estrogens, inhibition of lactation by androgens, and estrogen neutralization by progestin, may be mentioned. It would seem probable, therefore, that a physiological control of the over-active thyroid would be possible if a condition or substance acting as a chalone for the thyroid could be discovered.

I. *Spontaneous Remission of Acute Puerperal Hyperthyroidism*

Case 1. Mrs. A. L., aged 27 years, white, married. Her third pregnancy terminated normally on August 29, 1935; she nursed her baby. She was fatigued and intolerant to physical exertion, but did not have distinct complaints until after an acute sore throat on November 25, i.e., three months postpartum. After this the usual symptoms of severe thyrotoxicosis were pronounced. Amenorrhea associated with lactation was present. The basal metabolic rate on December 26, 1935 was + 56 per cent, pulse 136, weight 115 pounds; on January 8, 1936, the metabolic rate was + 54 per cent, pulse 100, weight 115 pounds. She was ordered to wean her baby on January 4, 1936. No iodine was given. The rapid subsequent fall of metabolic rate is indicated in figure 1. Menstruation occurred 31 days after cessation of nursing, i.e., on February 4, 1936. On February 14, after 41 days, the metabolic rate was + 6 per cent, the pulse 68, weight 118 pounds. Menstruation occurred regularly at 31 day intervals. In May of 1936 a test of responsiveness to thyrotropic hormone was carried out as indicated. No significant reaction occurred.

Interpretation: It seems possible that a thyroid inhibitory mechanism was developed during the readjustment from lactation to menstruation, that is, with the return of cyclic production of follicle stimulating pituitary hormone. That this condition had a chalone effect upon the thyroid is evidenced by the failure of the thyroid to respond to effective doses of thyrotropic hormone (see Starr 1937 and 1940). This suggests that the subsidence of hyperthyroidism was due not merely to the withdrawal of thyroid stimulation, a mechanism entirely possible, but to active inhibition by a chalone mechanism that persisted in force for some months.

II. *Remission Associated with Gonadotropic Treatment in Puberty*

Case 2. Miss G. DeF., a single Italian immigrant girl, 17 years of age, had lived in Chicago since the age of 7 years. At the age of 10 thyroid enlargement was noted. Her family physician administered Lugol's solution for three months when she was

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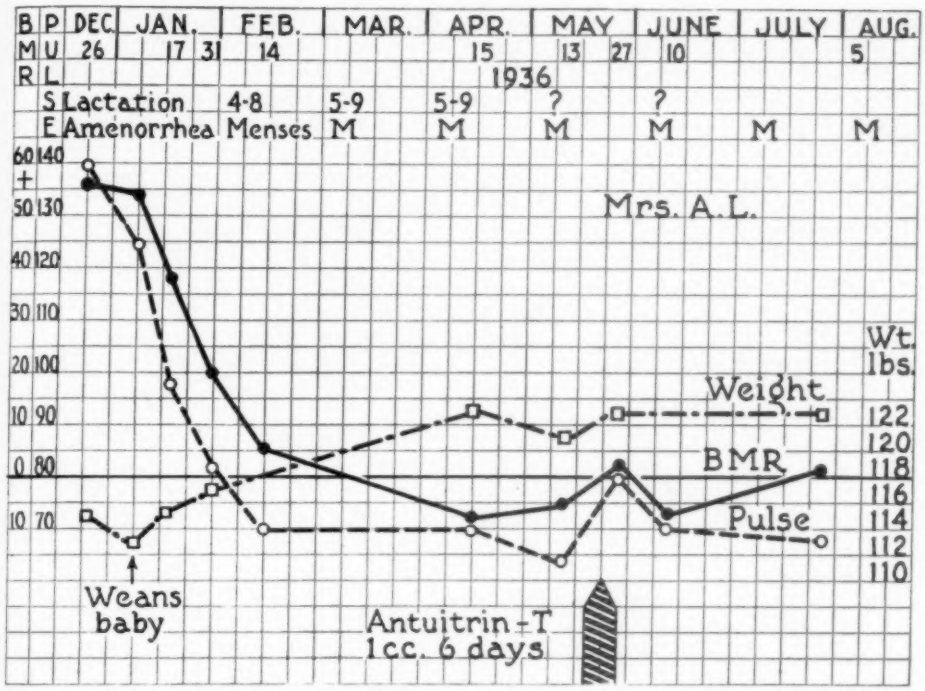


FIG. 1. (Case 1) Mrs. A. L. Example of remission of hyperthyroidism coincident with cessation of lactation and return of menstruation.

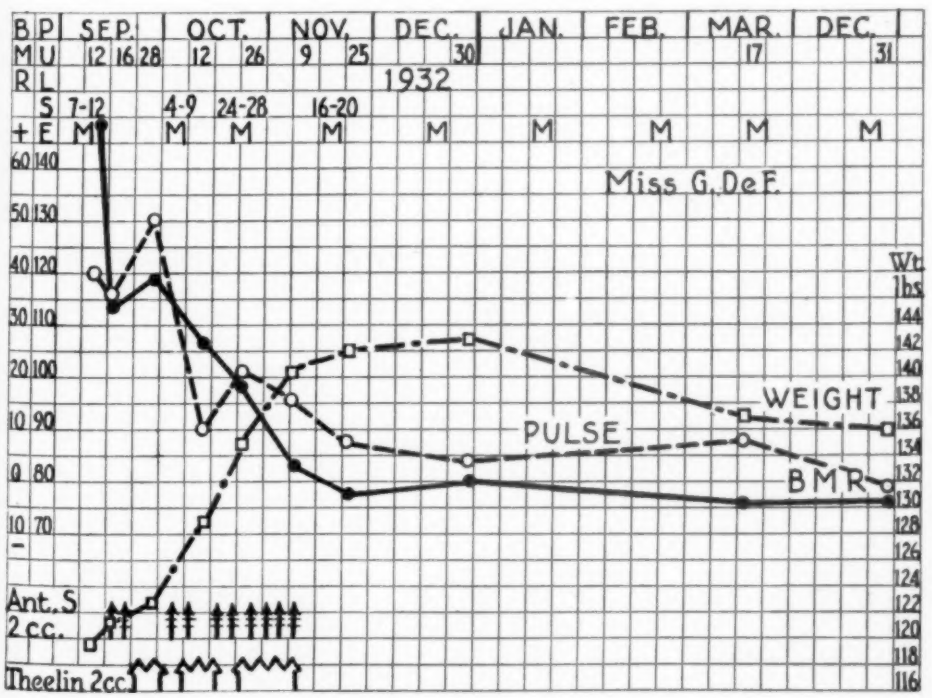


FIG. 2. (Case 2) Miss G. DeF. Example of remission of hyperthyroidism coincident with treatment with chorionic gonadotropin and theelin.

16 years of age. When admitted to the clinic in September 1932 she had had no iodine for six months. The thyroid was symmetrically enlarged to a slight degree. No exophthalmic signs were present; the pulse rate was 144. Other neuromuscular evidences of hyperthyroidism were present. Menstruation had been and continued regular. The first basal metabolic rate was + 67 per cent, pulse 132, weight 119 pounds. A control rate four days later, however, was + 34 per cent, pulse 120, weight 121 pounds. Antuitrin-S was given after menses and theelin before menses. The dramatic subsidence of hyperthyroidism is indicated in figure 2. When examined in December 1933, 15 months after admission, the patient's basal metabolic rate was — 4 per cent, the pulse 76, weight 136 pounds. She had no evidence of hyperthyroidism and had been doing factory labor for eight months.

Interpretation: It seems possible that the gonadotropic action of the anterior-pituitary-like hormone and the intermittent use of theelin induced an endocrine thyroid chalone mechanism. The pubertal state may be particularly favorable to this reaction. Subsequent experience was reported (Starr and Patton).

Clinical Studies

III. *Desiccated Thyroid Combined with Lugol's Solution*

The therapeutic administration of thyroid to patients with hyperthyroidism who already have an excess of thyroid hormone in their tissues is, nevertheless, plausible because of animal demonstration that substitution therapy inhibits the gland of origin (thyroid atrophy) and suppresses the pituitary production of tropic hormone for that gland (Kundy, 1928; Kuschinsky, 1933).

Case 3. Mrs. A. S. was observed in 1930, 1931 and 1932 (figure 3). Five control metabolic rates from August 1930 to February 1, 1931 averaged + 40 per cent. On Lugol's solution, without thyroid, the rate dropped to + 28 per cent. Lugol's solution was continued throughout the remaining months of observation. Desiccated thyroid, 4 grains daily, was begun on February 7. After one month of this combined medication the metabolism was only + 32 per cent. This suggests that the endogenous hormone was being reduced by the iodine solution as the exogenous thyroid was accumulating. Later, in April and May, the rate rose to + 58 per cent, as it may be supposed that the patient's thyroid was "escaping" from the Lugol's control. At the time of this increase the daily thyroid dosage was decreased to 2 grains and maintained at this level for three months, during which time the basal metabolism declined gradually to + 35 per cent; a further reduction in dosage to 1 grain daily was followed by a gradual decline to + 20 per cent in November 1931. Both medications were continued until the middle of May 1932. Three weeks after the discontinuance of the thyroid medication the metabolism was + 26 per cent.

Case 4. Mrs. J. D., aged 32 years; typical hyperthyroidism with exophthalmos and amenorrhea. She was observed on Lugol's and desiccated thyroid for a year before successful thyroidectomy. The control metabolism tests in March 1931 were + 34 per cent on the seventeenth and + 34 per cent on the twentieth. Large doses of desiccated thyroid—6, 8 and 4 grains a day—combined with Lugol's solution, were followed by an immediate drop, with a succeeding high plateau and, later, a depression which was finally succeeded by a recurrence when smaller doses of thyroid were used. The general course is similar to that in case 3.

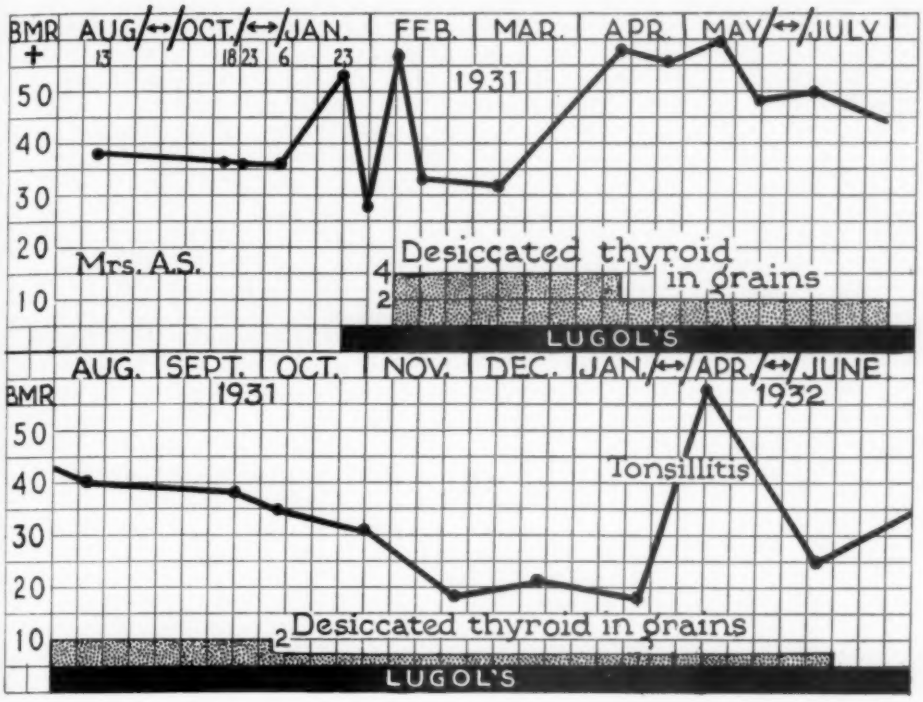


FIG. 3. (Case 3) Mrs. A. S. Example of effect of prolonged iodine and oral thyroid medication in hyperthyroidism.

Case 5. Mrs. A. P., aged 58 years, had had a goiter for five years, which had become toxic, with definite symptoms of hyperthyroidism during the past two years. She was observed from November 9, 1931 until February 19, 1932. Three control metabolic rates were + 41, + 25 and + 34 per cent. No iodine was administered. She was put on desiccated thyroid, 1 grain daily, on November 30, and this was increased to 3 grains a day on December 14. The basal metabolic rate dropped to + 26.5 per cent on December 28; the thyroid dosage was then increased to 5 grains a day and continued until February 19, 1932. The metabolic rate gradually dropped to + 22.5 per cent and her clinical symptoms improved considerably. She then left the city and was not seen again.

Case 6. Mrs. M. C., aged 26 years, showed mild hyperthyroid symptoms with slight suggestion of exophthalmos. A control metabolic rate was + 30 per cent. On June 19, 1931 she was placed on 6 grains of thyroid daily for three weeks; the basal metabolic rate rose to + 48 per cent and she lost eight pounds in weight, although her nervousness and emotionalism decreased somewhat. On July 10 the thyroid dosage was reduced to 4 grains a day; the metabolic rate continued to rise, and on July 24 it was + 50.4 per cent, although she stated that she felt better. The thyroid dose was again reduced—to 2 grains a day—and continued until October 5; during this time the metabolic rate gradually dropped to + 6.5 per cent on October 5 and her symptoms improved markedly. The thyroid medication was then stopped and she was put on 1½ grains of phenobarbital daily. Throughout the month of October she continued to feel fairly well but during the first week of November she had an attack of influenza which kept her in bed for 10 days. Following this she became restless and could not sleep. On November 23, 1931 the basal metabolic rate was still only + 6 per cent, but

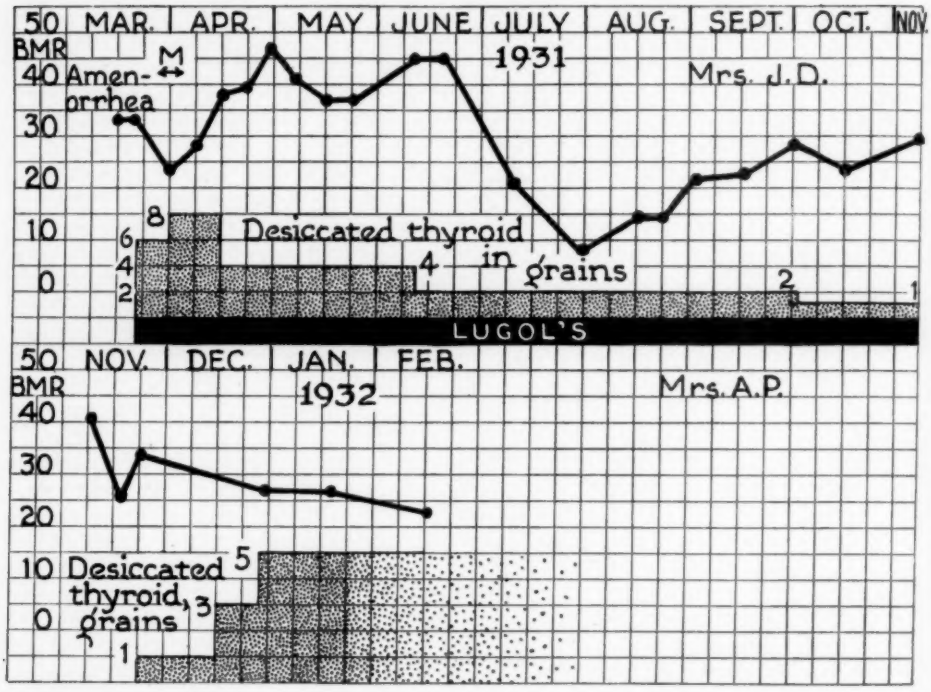


FIG. 4. (Case 4) Mrs. J. D. Example of effect of prolonged iodine and oral thyroid medication in hyperthyroidism.

FIG. 5. (Case 5) Mrs. A. P. Example of absence of additive calorigenic action of oral desiccated thyroid in hyperthyroidism.

she complained of diarrhea, sleeplessness, nervousness and, especially, marked exophthalmos. In fact, the exophthalmos was the dominating and most interesting feature in this case. When the patient was first seen there was only a suggestion of exophthalmos, although basal metabolic rates of + 30 and + 48 per cent were found, but, in spite of a gradual decrease in the metabolic rate and marked general improvement, the exophthalmos became progressively worse and a thyroidectomy was advised and performed in November, in spite of the normal basal metabolic rate and rather mild subjective symptoms, mainly because of the progressive exophthalmos.

Case 7. Mrs. K. T., aged 35 years, was under observation in our clinic from August 1931 until January 1935. When first seen she presented typical symptoms of hyperthyroidism, with definite eye symptoms; the basal metabolic rate was + 44 per cent. On August 10, 1931 she was put on Lugol's solution, 20 drops, and thyroid, 6 grains daily, and placed on a high caloric diet. This treatment was continued until September 18, 1931, when the thyroid was reduced to 3 grains and Lugol's to 10 drops daily; there had been little change in the metabolic rate since the beginning of treatment but the subjective symptoms had improved considerably. When seen on September 24 she complained of having suffered from severe headaches for a week, and the thyroid was again increased to 6 grains a day. On October 2 the basal metabolic rate was + 57 per cent, but the headaches had disappeared. This treatment was continued until October 9, when the thyroid was reduced to 3 grains and the Lugol's reduced to 15 drops daily, and whole pituitary, 3 grains a day, was added. She felt much better, although the metabolic rate rose slowly to + 49 per cent on October 16 and to + 58 per cent on December 21. The pituitary was discontinued on December

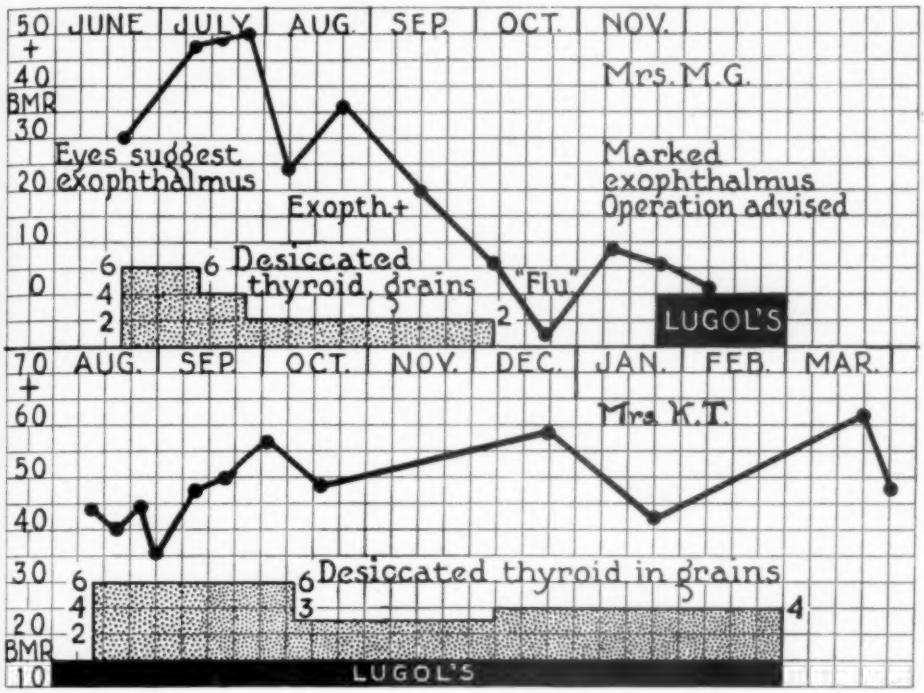


FIG. 6. (Case 6) Mrs. M. G. Example of falling basal metabolic rate and progressive exophthalmos with oral desiccated thyroid in hyperthyroidism.

FIG. 7. (Case 7) Mrs. K. T. Example of effect of prolonged iodine and oral desiccated thyroid in hyperthyroidism.

7, and the thyroid was again reduced to 4 grains daily. She gained weight and continued to work hard in spite of the increasing metabolic rate. On December 28 the thyroid dosage was reduced to 2 grains a day and continued at that amount until March 1, 1932, when all medication was stopped. The metabolic rate rose to + 64 per cent on March 21, and her subjective symptoms became aggravated. She was then put on Lugol's, 15 drops daily, and on a 2 per cent sodium fluoride solution, 30 drops daily. These were continued until April 11, at which time the thyroid gland seemed to be reduced in size but firmer in consistency, with a bruit over both lobes. The Lugol's solution was then increased to 20 drops daily. The patient did not return to the clinic until January 15, 1935, after an interval of nearly three years. She stated that during the year 1933 she gained weight up to 138 pounds (her weight on March 28, 1932 was only 108½) and felt very well and perfectly normal until May 1934. Her home surroundings were also much better during that period. In May 1934 she had an attack of some stomach or gall-bladder disease lasting about three weeks, during which time she lost 16 pounds. She said that she had been taking Lugol's, 20 drops daily, from September 1934 until three weeks before she returned to the clinic, and that she had not felt any different since stopping the Lugol's. Examination on January 15, 1935 showed no evidence of toxicity; her weight was 134¾ pounds, the pulse 92. There was no tremor. The thyroid gland was smooth, enlarged, firm and symmetrical, the skin warm; she was then in the seventh month of pregnancy.

Comment: Cases 3, 4 and 7 indicate the persistence of hyperthyroidism when large doses of iodine and desiccated thyroid are combined. Variations

in the metabolism over long periods of time present modifications of the usual course of hyperthyroidism under iodine (Starr 1927). Cases 5 and 6, hyperthyroidism treated with desiccated thyroid without iodine, are extraordinary. In case 6 the metabolic rate was raised from + 30 to + 50 per cent by massive initial thyroid medication and withdrawal was followed by remission, but this effect was accompanied by an increase of exophthalmos which, of itself, warranted thyroidectomy. Case 5 was not followed to conclusion. The control rates of + 40, + 25 and + 34 per cent are satisfactory. Gradual increase of thyroid medication was not followed by increased basal metabolic rate.

IV. *Effect of Thyrotropic Hormone in Hyperthyroidism*

All pituitary extracts containing the various pituitary tropic hormones tend to develop a specific immunity when used in animals for a prolonged period of time. Whether this immunity is brought about by the presence of specific antihormones in these extracts, as suggested by Collip, or by specific antibodies developed by the protein impurities of the extracts, is still a disputed point. That such an immunity does develop has been well established by numerous investigators and may be said to have been generally accepted. However, the role of the thyrotropic hormone, both in the development and in the course of human hyperthyroidism, has not been definitely established. In the cases presented here we have attempted to influence the course of human hyperthyroidism by injecting varying doses of thyrotropic hormone with the object of developing an immune state antagonistic to the disease.

Case 8. Mrs. J. A., 55 years of age, came to the clinic with an indefinite story concerning her thyroid disturbance. She stated that she was not nervous, had no heart consciousness and no excessive perspiration, but had noticed a small goiter; she had lost some weight as a result of dieting. The effect of Lugol's on the basal metabolic rate was rather questionable, as indicated in figure 8. From March 11 to April 23 she received no specific medication except cod-liver oil and phenobarbital, both of which were discontinued on the latter date. On May 29, 1935 she was given antuitrin-T,* ½ c.c. for four days; unfortunately, the immediate effect was not measured. The basal metabolic rate on June 18 was + 38.5 per cent, although she stated that she felt better than before the injections. One-half c.c. of antuitrin-T was given daily from July 10 to 16; on July 17 the metabolic rate was + 58 per cent, but the patient had no complaints; she was given elixir of phenobarbital which she continued to take until August 13. At that time she felt very well and all medication was stopped. The basal metabolic rate on October 11, 1935 was + 26 per cent, the pulse 72; she had no complaints whatsoever. She returned to the clinic on July 15, 1937, when her basal metabolic rate was + 27 per cent, without subjective symptoms. A third test of responsiveness to thyrotropic hormone was made. Basal metabolic rates on July 15 and 29 were + 27 and + 20 per cent respectively. Six injections of 1 c.c. each were given from August 11 to 18, 1937; the metabolic rate on August 19 was + 29 per cent, indicating non-significant variations in tests.

* Generously furnished by Dr. E. A. Sharp, Parke Davis & Company.

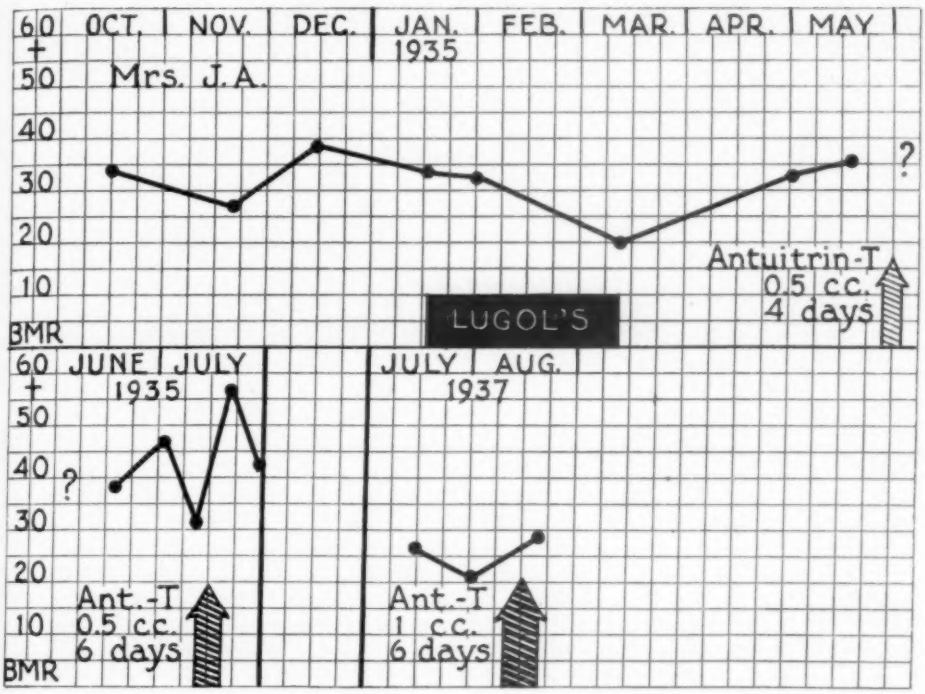
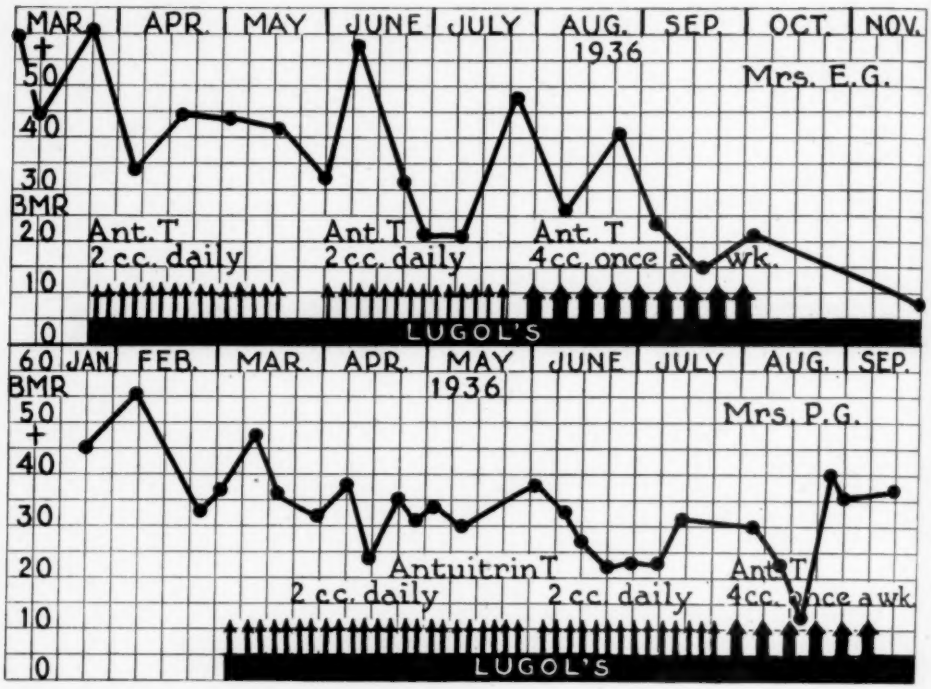


FIG. 8. (Case 8) Marked response to thyrotropic injections in 1935; absence of response to double the dose in 1937, suggesting development of chalone.

Comment: Response to thyrotropic injections in July 1935, from an average control rate of + 40 to + 57 per cent indicates lack of chalone as compared to the non-significant reaction in August 1937, when the clinical course was approaching recovery.

Case 9. Mrs. E. G., aged 37 years, presented herself at the clinic on February 2, 1936, with a large pulsating thyroid and subjective and objective symptoms of hyperthyroidism. The control basal metabolic rates were + 59.2 per cent on February 29, + 44 per cent on March 10, and + 62 per cent on March 21. On March 24 she was placed on Lugol's solution, 15 drops three times a day; phenobarbital, 3 grains a day; and antuitrin-T, 2 c.c. daily. This treatment was continued until May 16, 1936 (when the patient left the city for a vacation) with exception of the phenobarbital which was discontinued on April 7. During this period the basal metabolic rate fluctuated between + 34 and + 45 per cent and her subjective symptoms improved considerably.

On June 1 she returned, stating that she was feeling fine and had gained about 20 pounds in weight. The basal metabolic rate on that date was + 32 per cent, the pulse 96. She was again put on antuitrin-T, 2 c.c. daily. The metabolic rate on June 9 was + 58 per cent and on June 20, + 32 per cent. On the twentieth she returned to work, feeling very well. The antuitrin-T was continued daily until July 22, after which 4 c.c. were given once a week; the weekly injections were continued until October 3, and when last seen on February 7, 1939, she was still taking the Lugol's solution. There was a definite remission, both subjectively and objectively; the basal metabolic rate fluctuated, but at a much lower level, i.e., between + 10 and + 15 per



FIGS. 9 and 10. Examples of effect of prolonged treatment with thyrotropic hormone and iodine in hyperthyroidism. Note figure 11, that marked response to thyrotropic injections occurred in November 1934, August 1935 and September 1935, suggesting absence of chalone.

cent. She stated that she held a job which required much activity, walking and stair-climbing.

Case 10. Mrs. P. G., aged 44 years, presented a definite hyperthyroidism with slight exophthalmos. Two control basal metabolic rates were + 45 per cent on January 24, 1936, and + 56 per cent on February 4. She was placed on a high caloric diet, milk, and tincture of belladonna; this was continued until March 2 when the metabolic rate was + 36 per cent and the pulse 90. She was then put on antuitrin-T, 2 c.c. daily, and Lugol's solution, 5 drops three times a day. On this treatment the metabolic rate first rose to + 48.5 per cent, then gradually declined to + 36.5, + 31.5, and finally to + 23 per cent on April 13. After five weeks of treatment she seemed less toxic; the tremor disappeared; she ate and slept well; and the thyroid gland seemed smaller and harder. The antuitrin-T injections were stopped on May 27, started again on June 2 and continued throughout June, July and August. Although her subjective symptoms practically disappeared, the basal metabolic rate fluctuated between + 11 and + 40 per cent, and the pulse between 80 and 100. On September 8 the antuitrin-T injections were discontinued and thyroidectomy was advised; the basal metabolic rate at that time was + 35 per cent. On September 15 she reported that she did not feel as well as she had while taking the antuitrin-T. A thyroidectomy was performed on October 22.

Case 11. Miss D. H., aged 34 years, gave a history of thyroid disease at irregular intervals since 12 years of age. The degree of hyperthyroidism on admission to the clinic in May of 1934 was mild. Observation and treatment with various amounts of theelin and antuitrin-S did not lead to remission. The general average of

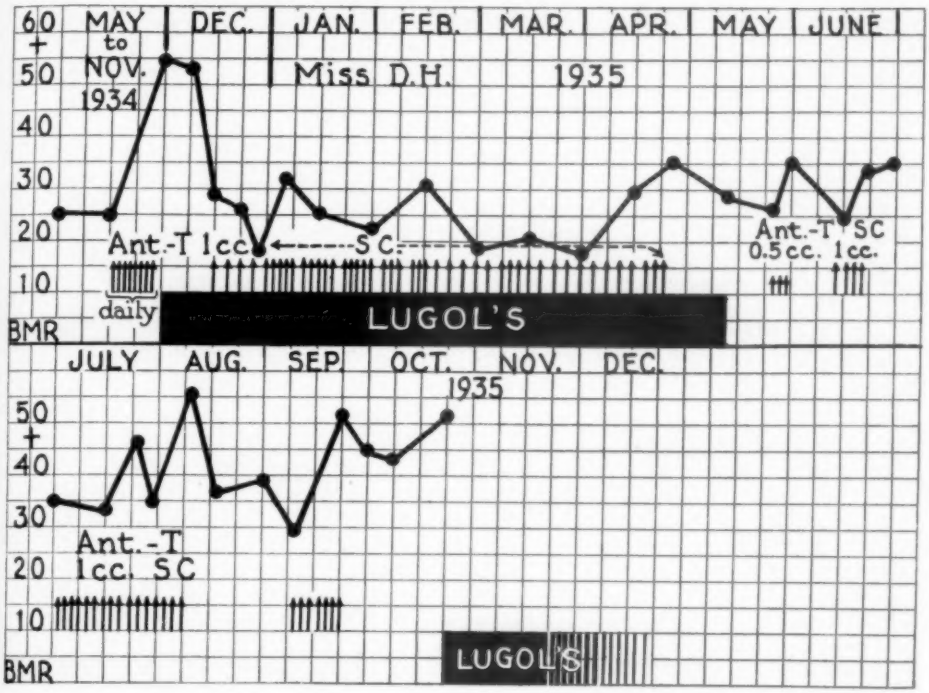


FIG. 11. Examples of effect of prolonged treatment with thyrotropic hormone and iodine in hyperthyroidism. Note figure 11, that marked response to thyrotropic injections occurred in November 1934, August 1935 and September 1935, suggesting absence of chalone.

basal metabolic rate determinations from May to November was + 25 per cent. Antuitrin-T, 1 c.c. daily for eight days, produced a sudden aggravation of symptoms and a rise of metabolism to + 55 per cent. Lugol's solution was immediately started and continued for five months. When the rate had returned to + 29 per cent antuitrin-T, 1 c.c. every other day, was given for four months. No inhibitory effect was produced. Lugol's solution was discontinued. Two months' treatment with antuitrin-T alone did not produce a sustained elevation of metabolism, but after a two week interval seven injections produced a rise of metabolic rate from + 30 to + 52 per cent.

This case demonstrates the exaggerated responsiveness of the hyperthyroid patient to thyrotropic hormone and that Lugol's solution will protect the patient's thyroid from the thyrotropic hormone. Moreover, prolonged treatment intermittently from December to September with thyrotropic hormone did not create antihormone which would affect the disease process or diminish the response to injections.

Case 12. Mrs. W. R., aged 29 years, presented herself on October 1, 1935, with a fairly well established hyperthyroidism, with slight exophthalmos. She gave a history of previous attacks of thyrotoxicosis followed by remissions. Three control basal metabolic rates of + 30, + 41 and + 30 per cent were obtained. On November 12, 1935 she was placed on Lugol's solution, 10 drops twice a day; this was continued throughout the entire course of treatment. Two weeks after starting the

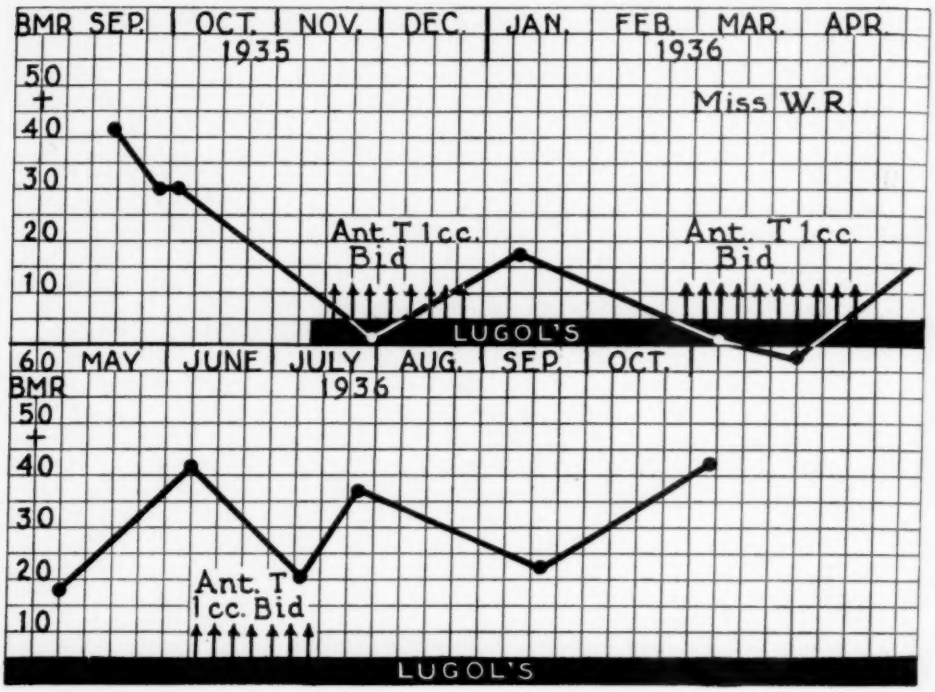


FIG. 12. (Case 12) Miss W. R. Example of subsidence and recurrence of hyperthyroidism during iodine treatment.

Lugol's there was a definite iodine remission, and the basal metabolic rate on November 26 was — 0.5 per cent. On the same day antuitrin-T, 1 c.c. twice daily, was added to the treatment and continued until December 24; it was again given from February 27 to April 14, 1936, and from June 10 to July 25. The basal metabolic rate fluctuated very markedly, as indicated in figure 12. On July 25, 1936 she stated that she felt very well but was tremulous when nervous. The pulse was 100, the thyroid firm and nodular. The general impression was that the thyrotoxicosis was under good control but not eliminated. Antuitrin-S, 1 c.c. daily for seven days, was then given in place of the antuitrin-T. On September 17, 1936 the basal metabolic rate was + 21 per cent; on October 28 it was + 44.5 per cent. When seen on March 6, 1937, the pulse was 92 and there was definite exophthalmos of the left eye, and marked tremor. Operation was advised, and a thyroidectomy was performed on April 5, 1937.

Comment: Patients 10 and 11, given prolonged treatment with thyrotropic hormone, were not benefited. Patient 12, given three courses of thyrotropic injections, each of a month's duration, at intervals of two months, was not controlled. Patient 9 gradually improved, as will some cases on iodine alone. Patient 8, in whom the disease very gradually and spontaneously subsided, apparently developed non-responsiveness to thyrotropic hormone as the disease regressed, in contrast to patient 11 who was still responsive after nine months of injections, when the disease was progressive.

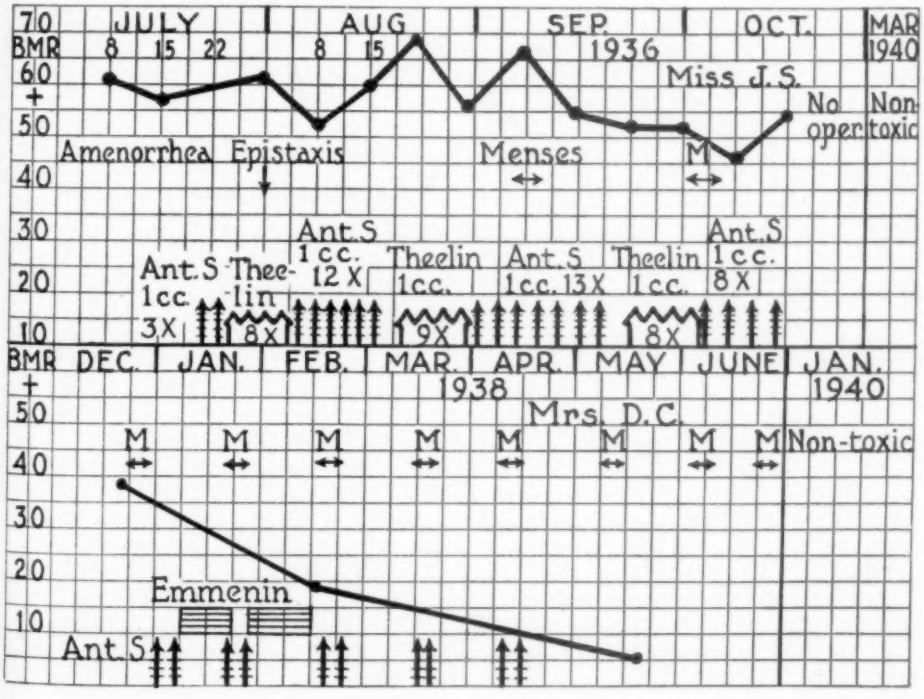
V. *The Effect of Ovarian and APL Hormone Injections*

Three examples of the effect of ovarian and anterior pituitary-like hormone therapy may be given as a commentary on earlier results (Starr and Patton, 1935).

Case 13. Miss J. S., aged 19 years. Thyrotoxicosis was severe but of only four months' duration; weight loss from 128 to 107 pounds; pulse 130; lid-lag present; bruit over an enlarged, symmetrical thyroid; menses diminished and delayed. Figure 13 indicates therapy with antuitrin-S (100 R. U. per c.c.) and theelin-in-oil (2000 I. U. per c.c.). Theelin was given before, and antuitrin-S during and following menses. After three months of this treatment she had regained 23 pounds but was still toxic; the bruit persisted; tremor was present; the pulse was 110. She then left the city to take care of an invalid parent. No operation was done. She returned 16 months later without thyrotoxic complaints, weight sustained, pulse 88, and no eye signs.

Comment: Antuitrin-S and theelin-in-oil were without immediate effect but may have induced a gradual remission.

Case 14. Mrs. D. C., aged 39 years, came to the clinic presenting all classical evidences of acute hyperthyroidism of nine months' duration. Monthly treatment with antuitrin-S (100 R. U. daily for six days) timed to follow the first day of the menstrual cycle for five months, and interval ingestion of Emmenin (240 day oral units) for two months were associated with a gain of 20 pounds in weight and a remission of symptoms which has persisted now for two years.



FIGS. 13 and 14. Two examples of subsidence of hyperthyroidism following treatment with chorionic gonadotropin and estrogenic substance.

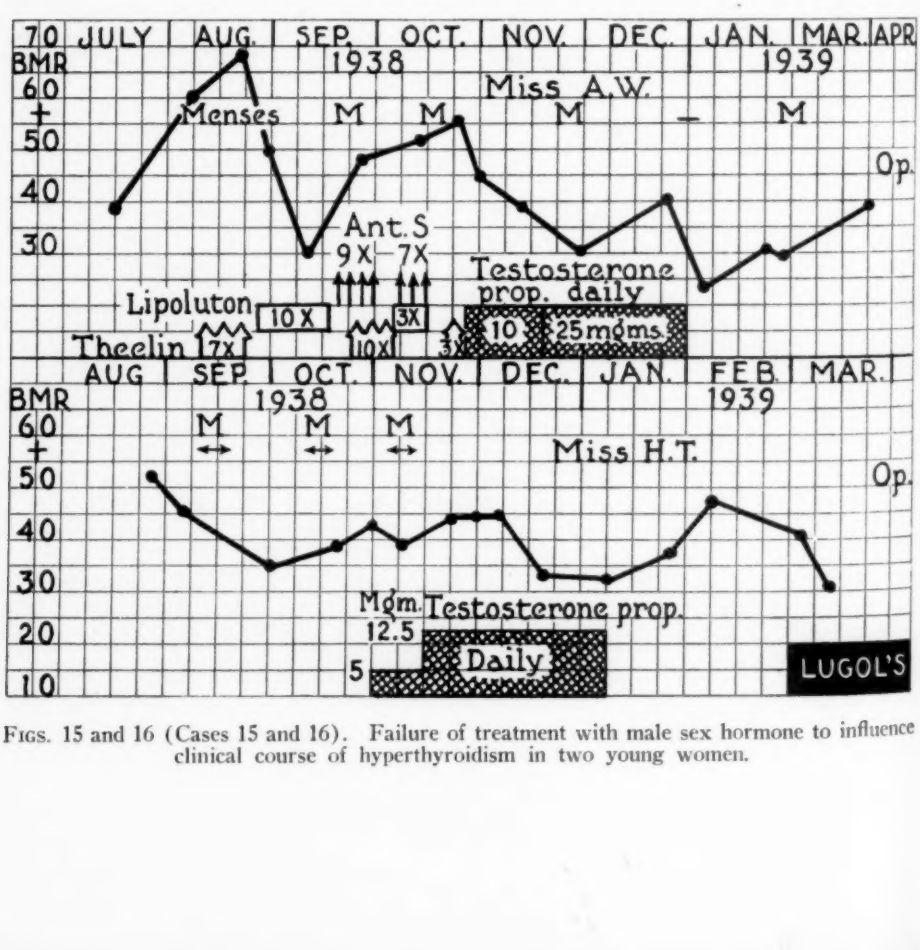
Case 15. Miss A. W., aged 30 years, came to the clinic in July 1938. She had a family history which included thyrotoxicosis in a sister, and a personal history of a previous attack of hyperthyroidism. She had a visible goiter, slight stare, a pulse rate of 128, and a basal metabolic rate of + 38 per cent. Antuitrin-S (500 R. U. per c.c.), Lipoluton (2 rabbit units per c.c.) and theelin-in-oil (10,000 I. U. per c.c.) were given successively as indicated in figure 15, from early August to late October, over two menstrual cycles, without benefit.

Comment: It may thus be seen that one of these three cases promptly improved during this type of treatment.

VI. *The Effect of Testosterone Propionate on Hyperthyroidism*

Sir Levy Simpson reported beneficial action from male sex hormone in hyperthyroidism. This had been suggested by the comparative infrequency of this disease in the male. Our experience is that it is without effect.

Case 15. Testosterone propionate (see figure 15) was given hypodermically to Miss A. W. for two months following the unsuccessful ovarian therapy. At the initiation of the androgen treatment the basal metabolic rate was + 44 per cent and after two months it was + 41 per cent. Menstruation in December was absent. After discontinuing the male sex hormone, menstruation returned and a temporary depression of metabolic rate did occur. Successful thyroidectomy was subsequently performed.



FIGS. 15 and 16 (Cases 15 and 16). Failure of treatment with male sex hormone to influence clinical course of hyperthyroidism in two young women.

Case 16. Miss H. T., aged 29 years, came to the clinic on August 19, 1938, with a fairly well established exophthalmic goiter and a basal metabolic rate of + 53 per cent. A second control metabolic rate on September 3 was + 42 per cent. On a high caloric diet, phenobarbital, and bed rest she gained weight, but her other symptoms failed to improve. On October 25 Perandren, 10 mg. every other day for 10 injections, was given; the dose was then increased to 25 mg. every other day for 34 injections, the last on December 30, 1938. There was a steady gain in weight and slight improvement in the subjective symptoms, but the basal metabolic rate fluctuated between + 34 and + 43 per cent and the pulse between 92 and 96, and on February 28, 1939, she was placed on Lugol's solution and prepared for thyroidectomy.

Case 17. Mr. J. S., aged 34 years, single, had an attack of hyperthyroidism in 1929, for which a thyroidectomy was done. Following the operation, nervousness and fatigue persisted until 1931. For six years he felt fairly well but then began to have attacks of diarrhea associated, since 1938, with nervousness, fatigue and nausea. On September 27, 1938, he presented symptoms of a mild hyperthyroidism, with a basal metabolic rate of + 20 per cent and a pulse of 120. He had been taking iodine before coming to the clinic; this was stopped on admission and he was placed on phenobarbital, ½ grain three times a day, and a high caloric diet. The basal metabolic rate rose to + 38 and + 36 per cent and the symptoms became aggravated. On November 1 testosterone propionate, 10 mg. three times a week, was added to the above régime. On November 29 he reported that he felt better although he was still weak. The testosterone dosage was then increased to 25 mg. three times a week; these injections were continued until January 3, 1939, by which time he had received 12 injections of 10 mg. and 8 injections of 25 mg. (see figure 17). All injections were then discontinued, the only medication being phenobarbital and cod-liver oil. The basal metabolic rate continued to fluctuate between + 17 and + 30 per cent and he was still weak and nervous. Accordingly, on February 28 he was placed on Lugol's solution and prepared for thyroidectomy.

VII. *Vitamin A in Hyperthyroidism*

The relationship of vitamin A to the thyroid gland and its hormone, thyroxin, has recently attracted a great deal of attention. Many investigators, both in the United States and on the Continent, have devoted much time, energy and ingenuity to the study of this problem. All of these studies point to the existence of an antagonism, chemical or physiologic in nature, between vitamin A and thyroxin. Almost all the effects of the latter are counter-balanced and neutralized by the former and vice versa; the intoxication of the animal produced by the feeding of enormous doses of vitamin A can be prevented by the simultaneous feeding of thyroxin.

How far this finding is applicable to human hyperthyroidism is problematic. Several prominent German clinicians, such as Wendt, Falta, and Dietrich, have treated Graves' disease with huge doses of vitamin A in the form of a special German preparation, "Vogan." They report excellent results in the majority of their cases—gain in weight, lowering of the basal metabolic rate, slowing of the pulse, and general improvement in subjective symptoms. Unfortunately, their cases were poorly controlled. We are presenting here a case of recurrent Graves' disease in which we used even

larger doses of vitamin A than the German clinicians, in the form of a specially purified cod-liver oil furnished to us by the Abbott Laboratories.*

Case 18. Mrs. H. B., aged 49 years, a widow, had had an attack of toxic goiter in 1932, which gradually subsided. In 1935, after the death of her husband, symptoms recurred in a much aggravated form, and she was subjected to thyroidectomy. For about a year after the operation her general condition continued to improve although she was unable to gain weight. Late in 1936 she developed hot flashes with a recurrence and aggravation of all her thyroid symptoms. When first seen at the clinic in

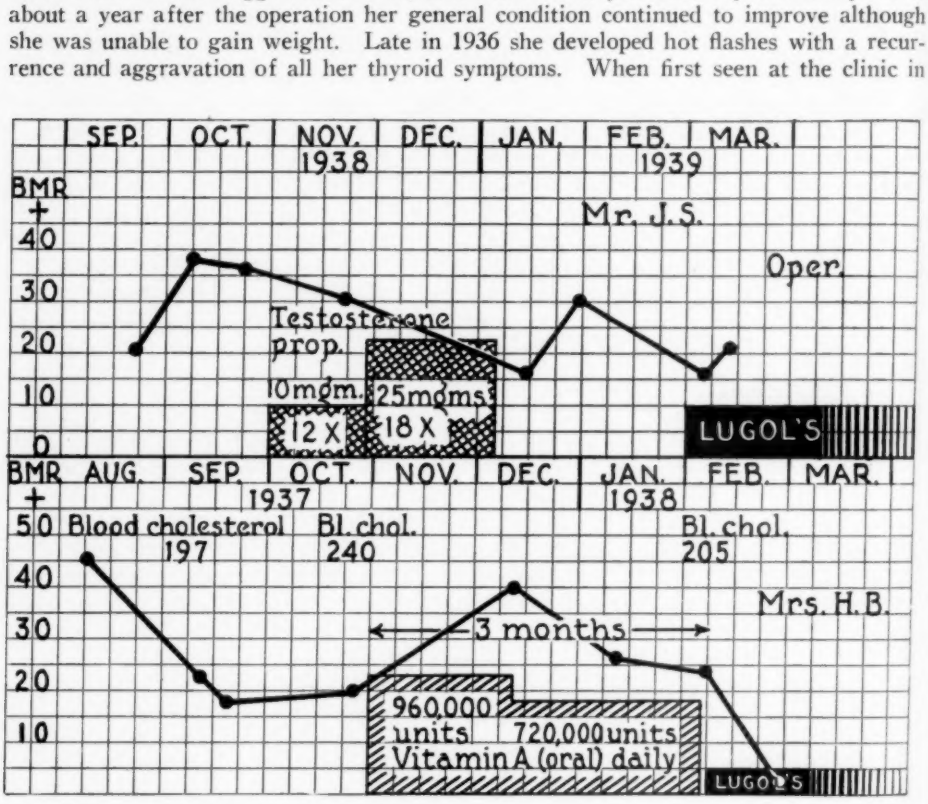


FIG. 17. (Case 17) Mr. J. S. Failure of testosterone to modify course of hyperthyroidism in a male patient.

FIG. 18. (Case 18) Mrs. H. B. Massive dosage of oral vitamin A for three months without effect on clinical course of hyperthyroidism.

May 1937 she had a pulse of 114, a basal metabolic rate of + 50 per cent, enlargement of the right lobe of the thyroid and marked stare. She was placed on phenobarbital, 2 grains daily, and a high caloric diet; this was continued from May 11 to June 29. The response was poor. On June 24 the pulse was 112, and the basal metabolic rate + 33 per cent; she had gained no weight and was still very nervous and tremulous. On June 29 she was placed on theelin, 1 c.c. daily, which was continued until August 9, without any benefit; on that date her pulse was 120, the metabolic rate + 46.5 per cent; her weight had increased from 111 to 118 pounds. She was again given a high caloric diet, karo syrup sandwiches, and phenobarbital. For a while she felt better, and gained another pound or two; the metabolic rate decreased to an average + 21.2 per

* We wish to thank Dr. Carl Nielsen of the Abbott Laboratories for his generous supply of vitamin A concentrate.

cent. However, on November 2 she became worse, complaining of insomnia, extreme nervousness and irritability, heat intolerance, excessive perspiration, and diarrhea. She was then placed on vitamin A, 960,000 I. U. daily by mouth. This was continued throughout November, December, January (1938) and until February 8; the response was very slight; there was very little gain in weight (120 to 122 pounds); the pulse was only slightly reduced (100–96); and the basal metabolic rate was + 40.5 per cent on December 9, + 26.2 per cent on January 11, and + 23 per cent on February 8. There was, however, considerable improvement in her subjective symptoms. The vitamin A was discontinued on February 8, and she was placed on Lugol's solution in preparation for surgery; the metabolic rate dropped to + 3 per cent in two weeks. A thyroidectomy was performed on June 8, 1938.

In comparing this case with those reported in the German literature it is especially interesting to note the blood cholesterol findings in this patient. The German clinicians stressed particularly the rise of the blood cholesterol and the consequent considerable gain in weight in their patients in response to the vitamin A treatment. We failed to find such a rise; in fact, we found a decrease in the blood cholesterol. Before the initiation of the vitamin A treatment, when our patient was receiving only phenobarbital and a high caloric diet, the blood cholesterol rose from 197 mg. on June 22, 1937 to 240.5 mg. on November 2, while after three months' treatment with vitamin A the cholesterol declined to 205 mg. on February 7, 1938.

VIII. *Vitamin C in Hyperthyroidism*

There are a great many conflicting reports concerning the relationship of vitamin C to the thyroid. Some investigators claim to have found hyperactive and hypertrophied thyroids in animals (guinea-pigs) that have been kept on a vitamin C-free diet, and further claim that they have been able to prevent the hyperthyroidism ordinarily produced by thyrotropic hormone injections by the simultaneous feeding of vitamin C. They contend, therefore, that vitamin C has a specific antithyrotropic effect which it exerts upon the thyroid. All of these claims are countered by another group of observers who have used the measurements of the cell heights as a criterion and who claim that the cell height of the thyroid of scorbutic animals is so slightly changed that one is not entitled to speak of a hyperactive thyroid. Similarly, they have been unable to inhibit the effects of thyrotropic hormone upon the thyroid even by huge doses of vitamin C.

In the case presented here we have attempted to determine the effects of huge doses of vitamin C upon the basal metabolic rate, blood cholesterol and weight curve of human hyperthyroidism; we also wished to ascertain whether the rise in blood vitamin C and in urinary and fecal vitamin C excretion, which always follows the ingestion of such huge quantities of vitamin C would be offset by the hyperactive thyroid. We are grateful to Professor Chester Farmer of the Department of Chemistry, Northwestern University Medical School, who provided ascorbic acid and carried out chemical determinations.

Case 19. Mrs. J. R., aged 30 years, gravida 7, para 4, youngest child six months old. After the birth of her second child four years previously she had a so-called "nervous breakdown"—probably acute hyperthyroidism—with loss of weight from 125 to 89 pounds, followed by gradual recovery in 18 months. It should be noted that two completed pregnancies occurred after this illness. Symptoms of hyperthyroidism began again during this last puerperium. The baby was weaned at four months with return of menses, but in contrast to Case 1 the hyperthyroidism was not abated. On examination she had a pulse of 120, marked tremor, lid-lag, flushing and sweating. After two months' observation the basal metabolic rate determination averaged about + 33 per cent. Three grams of cevitamic acid were given by mouth daily in divided doses, for a month, with two short interruptions as indicated in figure 19. Blood cevitamic acid level rose from 0.25 mg. per cent to a peak of 2.5 mg. per cent, but maintained a concentration of 1.75 mg. per cent. From 1000 to 1400 mg. were measured per 24 hours in the urine. Fecal assays were negligible. No amelioration of hyperthyroidism or reduction of the basal metabolic rate occurred. Thyroidectomy was successfully performed on July 27, 1939.

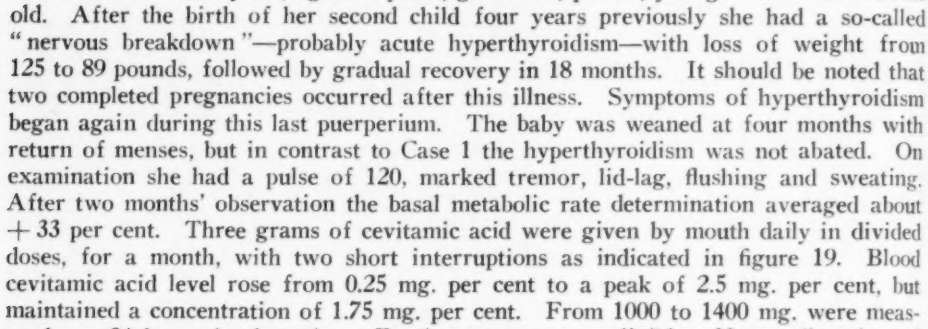


FIG. 19. (Case 19) Mrs. J. R. Massive oral medication of vitamin C for one month without effect on basal metabolic rate in hyperthyroidism.

SUMMARY

Abrupt and complete subsidence of acute hyperthyroidism in a young mother occurred when she weaned her baby (figure 1). The cure of a girl during adolescence, coincident with injections of chorionic gonadotropin and aqueous estrogenic substance, was very similar (figure 2). Desiccated thyroid was given to five patients; it was combined with Lugol's solution in three of these (figures 3, 4 and 7) without benefit; 5 grains a day alone failed to raise the rate in one case (figure 5); in another case (figure 6) the rate subsided rapidly but exophthalmos increased.

Thyrotropic hormone in one patient was calorigenic during one phase of the disease (figure 8) but apparently without effect two years later when the hyperthyroidism was milder. In four patients who were given prolonged treatment with thyrotropic hormone and Lugol's solution, no remission was induced (figures 9, 10, 11 and 12). One of these patients remained sensitive to the thyrotropic action after 10 months of intermittent treatment. This

suggests that development of an antihormone or antibody in this patient did not occur. Two patients treated with chorionic gonadotropin became nontoxic (figures 13 and 14). Two young women and one man with hyperthyroidism (figures 15, 16 and 17) were not improved by testosterone propionate. One patient was treated with very high dosage of vitamin A (figure 18) with no effect on the metabolic rate which was then promptly reduced by Lugol's solution. Massive dosage of vitamin C was likewise without effect on the metabolic rate in another patient (figure 19).

Conclusion

The existence of a chalonic mechanism acting to restore thyroid activity to normal is suggested by known physiological equilibria. An occasional case of hyperthyroidism subsides rapidly as though such a mechanism were in operation. Attempts to induce such a chalone by administration of desiccated thyroid, thyrotropic hormone, vitamin A, vitamin C and testosterone propionate, have been ineffective. Treatment with chorionic gonadotropin has been accompanied by remission of hyperthyroidism in a number of cases.

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ACUTE HEPATITIS OF ALCOHOLISM: A CLINICAL AND LABORATORY STUDY *

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In an earlier study several liver function tests were carried out upon patients in whom a diagnosis of cirrhosis had been previously confirmed, both by peritoneoscopy and liver biopsy. The excretion of bromsulfalein was found to be the most accurate test to measure the degree of liver damage.[1] This opinion is in accordance with the experience of other workers.[2, 3] However, the pathological diagnosis and the estimate of liver function are not always in agreement because some patients, having a high retention of bromsulfalein, die of subacute cirrhosis before marked atrophy occurs; others may survive until marked atrophy of the liver parenchyma has taken place. Furthermore, satisfactory bromsulfalein excretion may occur although the organ is in a state of extensive fibrosis. From an analysis of the causes of death, whether due to pneumonia, gastrointestinal hemorrhage, or liver insufficiency, it appeared that those having either early or advanced cirrhosis died of the same immediate causes in relatively the same proportions. Nevertheless, the bromsulfalein excretion test was of definite value in detecting liver damage, and it disclosed that some acute alcoholics, without jaundice, peripheral neuritis, or a palpable liver, were found to retain an abnormal amount of the dye at the end of half an hour.

The purpose of this study was to determine, by repeated testing of those alcoholics who had an initial dye retention, the time necessary for the liver function to return to normal. In previous studies it was found that those who had been drinking for less than two weeks failed to show abnormal bromsulfalein tests. The high caloric content of alcoholic beverages, particularly fortified wines, automatically reduced food consumption to meager amounts. Because these patients imbibed alcohol they did not wish to eat and, therefore, after a period of time suffered a depletion of the liver's protein, carbohydrate, and vitamin reserves, thus leaving the organ susceptible to injury. This sequence of events has been experimentally demonstrated in animals, and it is inferred that it occurs in men. For instance, Goldschmidt, Vars, and Ravdin [4] tested the protective value of different foodstuffs fed to chloroformed mice. They showed that a high protein diet was definitely protective, and served to minimize the destructive action of hepatic toxins. The value of carbohydrate feeding seems to be its rôle of protein sparing, leaving proteins to neutralize the toxic action of chloroform. Messinger and Hawkins [5] maintain that a high protein diet protects dogs against liver injury from large doses of arsphenamine. Finally, rabbits fed on a

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balanced diet, with the exception of some components of yeast, were observed by Rich and Hamilton [6] to develop a cirrhosis resembling Laennec's cirrhosis in man. It is not surprising therefore that a certain number of the poorly nourished alcoholics whom we investigated were found to suffer from hepatitis, although in the majority of them the liver injury was not sufficiently marked to be clinically recognizable.

There is apparently a relationship between the increased admissions to the Los Angeles County Hospital of patients with cirrhosis, and the repeal of prohibition. Evans and Gray [7] found among 17,879 autopsies performed

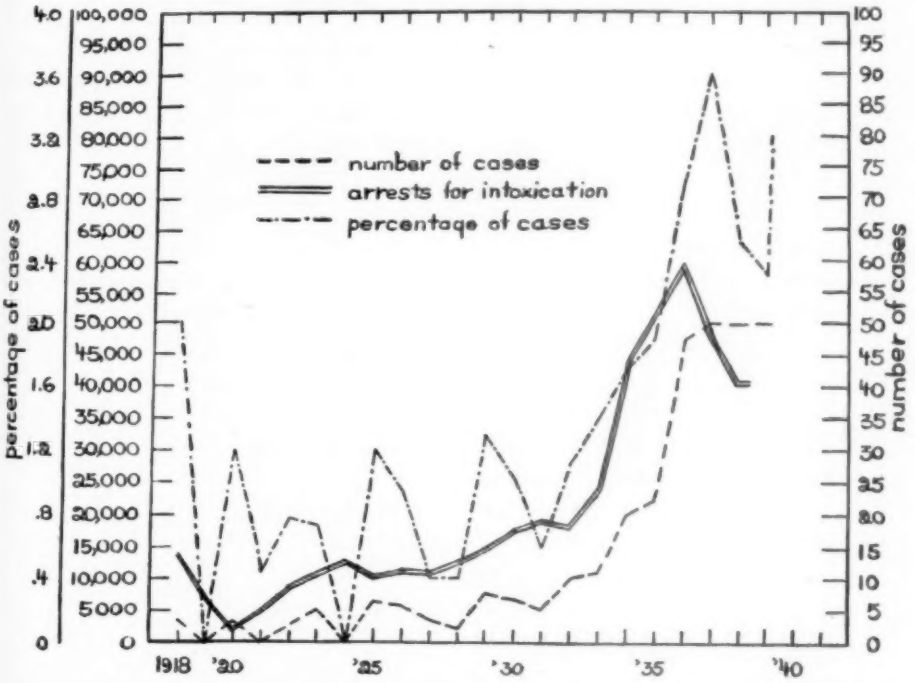

CHART 1. Represents the relationship between the number of arrests by thousands in the City of Los Angeles and the incidence and percentage of all cases having postmortem examination in the Los Angeles County Hospital.

between January 1, 1918 and May 1, 1937, 217 instances of cirrhosis of the liver. During the prohibition years, 1918 to 1932 inclusive, there were 62 instances of cirrhosis, or 0.65 per cent of all autopsies, as contrasted with the post-prohibition era, from 1933 to May 15, 1937, during which 155 instances of cirrhosis (1.84 per cent of all autopsies) were found. This is a three-fold increase (chart 1). A recent compilation, from May 1937 to March 1, 1940, of 5908 autopsies shows that in 152, or 2.5 per cent, cirrhosis of the liver was found, or a four-fold increase of cirrhosis over the prohibition era. During the fiscal year 1936–1937 there were 49,383 arrests made for drunkenness representing 64 per cent of arrests for all charges by the Los Angeles Police Department (chart 1).

Procedure

The selection of alcoholic patients was not made at random, since the objective was to isolate those who had a dye retention. The patients were then rechecked at intervals until the retention had disappeared. The ones selected were shaky and on the verge of delirium tremens. They had been drinking for not less than two weeks and some had been drinking steadily for six weeks. The determination was done according to the following technic. The amount of bromsulfalein injected intravenously was 5 mg. per kilogram of body weight, and a blood sample was withdrawn exactly 30 minutes later. The blood specimen was poured into an oxalated receptacle and centrifuged. A measured amount of serum was removed, diluted with an equal amount of acetone, shaken, and again centrifuged. After alkalinizing, the specimen was checked by the colorimetric method and the reading was multiplied by two.

Results

The present study represents a total of 40 bromsulfalein tests made on 25 alcoholics. Fourteen of the men were found to retain 5 per cent or more on the first test, and were regarded as having a disturbance of liver function. Of these 14 patients, one had 30 per cent, five had 20 per cent, and eight had from 16 per cent to 5 per cent dye retention. Six of the patients were followed with interval testing until the dye test returned to normal. The other patients could not be followed because they left the hospital before their liver function tests had returned to normal.

The following brief abstracts of three of the cases illustrate some of the clinical aspects of alcoholics with a temporary retention of bromsulfalein.

Case Reports

Case 1. J. B., white, 32 years old, had been previously admitted to the hospital on November 15 for the removal of an epithelioma of the face; a positive blood Wassermann reaction was obtained. He had been drinking steadily for six weeks, and for one week before his arrest had suffered from nausea and attacks of vomiting. For three days he had a mild diarrhea and complained of a dull aching pain in the epigastrium. There was no icterus, nor was there any tenderness of the calves of the legs on pressure. The tongue was clear and atrophy was absent. The liver could not be palpated. When the bromsulfalein test was done, 20 per cent of the dye was retained, and four days later the results of the test were unchanged (chart 2, J. B.). On February 16, one week after he was first seen, peritoneoscopic examination and liver biopsy were done by Dr. John Ruddock. The preoperative diagnosis was alcoholic hepatitis. The report was as follows: "No peritoneal fluid was seen; all visceral surfaces appeared normal. Gall-bladder and appendix were normal. The liver was slightly enlarged, its edge is sharp; it is smooth, brown, and soft in consistency. Conclusion: no pathologic changes seen."

Examination of the liver biopsy showed that the hepatic architecture was slightly disturbed. The periportal connective tissue was only very moderately increased, if at all. The amount of fat in the liver cells was increased and was more abundant in the

centers of the lobules (figure 1). There was a mild inflammatory change in the liver as evidenced by the moderate number of mononuclear cells and an occasional polymorphonuclear leukocyte in the periportal connective tissue. An occasional necrotic liver cell was seen and a considerable variation in the size of the liver cell nuclei, with many of them appearing rather large and deeply stained. The diagnosis was: "Mild toxic hepatitis and fatty liver." Eight days following peritoneoscopy another bromsulfalein test was done which was normal.

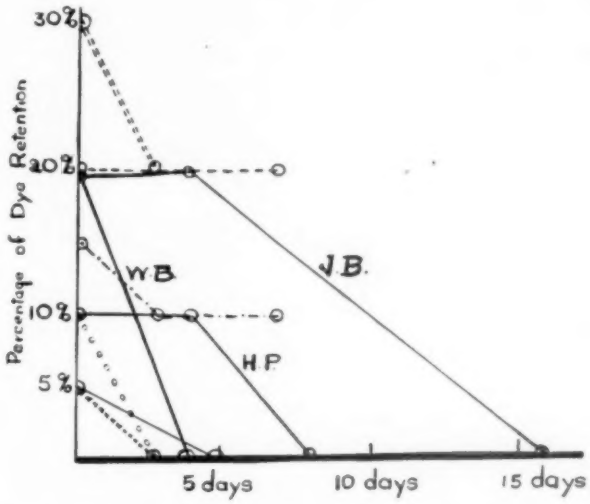

CHART 2. Follow-up by means of the bromsulfalein liver function test upon alcoholics having a half-hour retention.

In this case there was evident correlation between the pathological interpretation and the bromsulfalein test. Liver damage was present and was associated with physiological dysfunction, since the reticulo-endothelial cells were unable to rid the blood stream of the dye.[8]

Case 2. H. P., white, 55 years old, for five weeks prior to admission had drunk from one and one-half to two quarts of wine daily. When first seen, March 10, 1940, the blood Wassermann reaction was negative. His bromsulfalein test was reported as showing 10 per cent dye retention, and when repeated four days later was again found to show 10 per cent retention (chart 2, H. P.). Peritoneoscopy was done by Dr. John Ruddock, March 14, and the following notes were made: "The liver edge was 2 cm. below costal border. There was no edema, and no fluid. The liver was reddish brown in color and of usual size; its peritoneal surface was smooth. There were numerous adhesions around the cecum. Impression: Grossly normal liver." The microscopic examination of a liver biopsy revealed normal findings. Three days after this operation the dye test was normal.

In this particular instance there is a lack of agreement between the biopsy findings and the results of the liver function determinations. Ten per cent dye retention test was present the same day that peritoneoscopy was done, indicating definite impaired physiologic function, but no pathological changes were observed. Undoubtedly there may be impairment of the biliary ex-

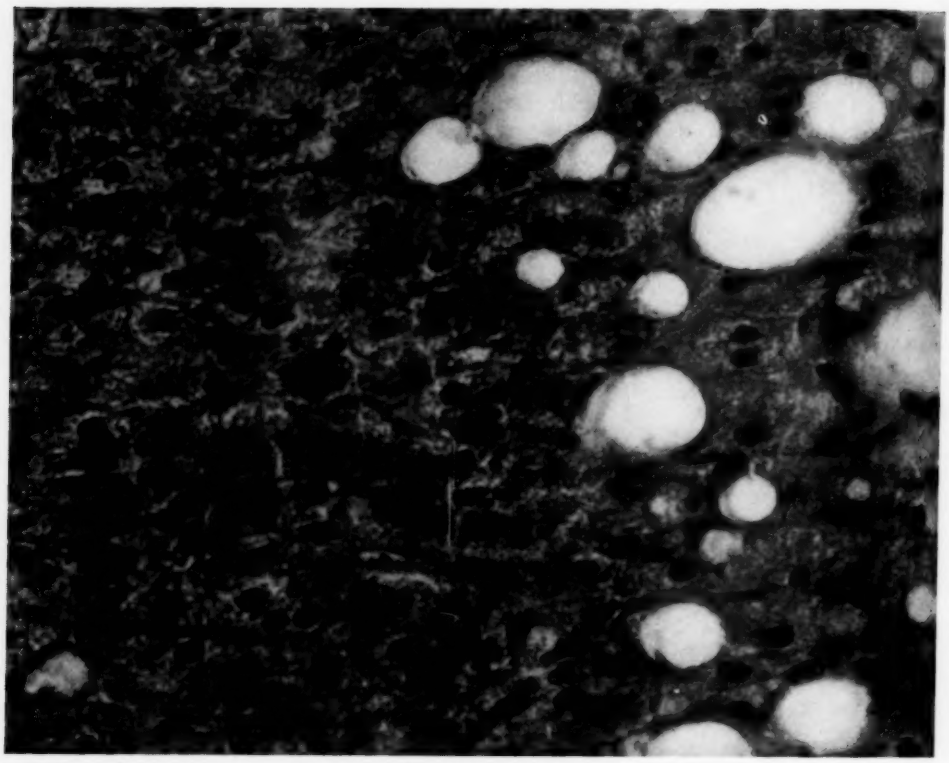

FIG. 1. (Case 1.) Photomicrograph (× 550) liver biopsy, showing slight fatty infiltration and mild inflammatory changes.

cretory system prior to recognizable morphological changes of the hepatic tissues.

Case 3. W. B., white, 57 years old, was first seen on June 20, 1940, after he had been drinking about one quart of whiskey a day in addition to wine and beer for 15 days. He had eaten very little. He was extremely tremulous and feared having delirium tremens. A bromsulfalein test was made, and 20 per cent of the dye was retained. The test was repeated four days later and there was less than 5 per cent of dye retention (chart 2, W. B.).

The rapid decline from 20 per cent to less than 5 per cent retention within four days was probably due to the comparatively short duration, 15 days, of continual intoxication. The histories of the other three patients who were followed until the test returned to normal are not presented here in detail, but reference to chart 2 will illustrate the rapid restoration of liver function of these patients, beginning with their abstinence from alcohol and resumption of a regular diet.

DISCUSSION

Using tests other than the one employed in this study for estimating liver injury in acute alcoholism, Wallace [9] found in 17 patients suffering from

acute alcoholism that the serum bilirubin concentration ranged from 0.85 to 2.1 units, and in five patients he observed abnormal urobilinogen concentration which ranged from dilutions of 1:90 to 1:350. The one patient in this group who was most toxic became well, according to the results of the tests, after a period of five days. After a preliminary two-day fasting period, MacNider [10] subjected dogs to either a 12- or 24-hour period of severe alcoholic intoxication and found evidence of lobular damage to the liver. At the end of 12 hours the liver was pale and the lobulations were not distinct. Microscopic examination revealed marked edema of the liver cells in the peripheral half of the lobules and accumulations of stainable lipoid material. MacNider noted that the nuclei in the peripheral portions were hypochromatic. Sections of the liver of the 24-hour intoxicated dogs contained evidence of edema involving the entire lobule, which was most intense in the outer zone. The capillary spaces were obliterated and the central veins compressed. Grossly the organ was enlarged and grayish-white in color. The livers of control dogs which had been deprived of food for two days and then given an ether anesthesia for three hours were found by microscopic examination to contain small drops of lipoid substances in the periphery of the lobule. When liver function was tested with phenoltetrachlorphthalein, the dogs which had been subjected to a 12-hour intoxication were found to retain from 7 to 10 per cent of the dye at the end of one hour during the first day, but had no retention when tested on the third day. Dogs that had been intoxicated for 24 hours were found to retain from 14 to 17 per cent of the dye, and on the third day the test became negative.

The experimental investigation cited above indicates that liver damage as revealed by the dye retention test may occur from alcohol and anesthetic administration, and may disappear if the damage is not too severe. The results of this study also emphasize that the bromsulfalein liver function test is sensitive enough to pick up various degrees of liver damage, either with physiologic dysfunction alone or associated with definite pathological changes. Not all alcoholics show such liver dysfunction, but only about one out of every 300 of the cases which were observed during the course of this investigation.

Conclusions

1. Some alcoholics after prolonged and continuous drinking have liver impairment as shown by the bromsulfalein test.

2. The earliest discernible change in the livers of such patients is a decrease in the physiological efficiency of the reticulo-endothelial cells which remove the dye from the circulation. Biopsy made in two cases showed no pathological disturbance in one, and in the other evidence of only mild toxic hepatitis with fatty infiltration, although dye retention was present in both.

3. The 25 alcoholics who had abnormal bromsulfalein tests are regarded as being cases of hepatitis unrecognized clinically. A certain number of this

group have a progressive liver deterioration leading eventually to Laennec's cirrhosis.

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THE SIGMOIDOSCOPIC DIAGNOSIS OF PERIARTERITIS NODOSA *†

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THE diagnosis of periarteritis nodosa during life is difficult. Since the classical descriptions of the disease by Rokitansky in 1852 and Kussmaul and Maier in 1856 more than 200 cases have been reported, but relatively few of these were diagnosed intra vitam (31 cases up to the end of 1935).[1] The purpose of the present communication is to report one such case in which the diagnosis was definitely established by sigmoidoscopy and confirmatory evidence obtained at necropsy. Two additional cases of relevant interest will also be described because they provided excellent clinical and pathological material for a better understanding of our observations at sigmoidoscopy. Detailed laboratory findings are given where they appear to be of interest in connection with the underlying clinical and pathological condition.

Case 1. C. D., female, aged 45 years, was admitted to The Bronx Hospital on February 16, 1936, with a history of asthma following an upper respiratory infection in September 1935. A physician informed her that a skin test had revealed a sensitivity to dust. Two weeks before admission the patient contracted another "cold" with aggravation of her asthma. Physical examination revealed an emphysematous chest and the presence of sibilant and sonorous râles. Skin tests revealed a slight reaction to dust, oak and birch. A polypoid mass was seen blocking the right nasal meatus and there was a pan-sinusitis on the same side. On March 4 the antrum was punctured, but no pus obtained.

Laboratory examinations were as follows: The blood Wassermann and Kahn tests were negative. A blood count on February 17 revealed hemoglobin 86 per cent, erythrocytes 5,400,000 per cu. mm.; leukocytes 38,400 per cu. mm., polymorphonuclear neutrophiles 83 per cent, band forms 6 per cent, lymphocytes 9 per cent, monocytes 2 per cent. Blood chemical tests were normal on the same day. The sputum was slightly blood-tinged on February 20, but otherwise not abnormal. The bleeding time was 2 minutes and coagulation time 4 minutes. On March 4 the leukocytes were 11,500 per cu. mm., polymorphonuclear neutrophiles 76 per cent, band forms 4 per cent and lymphocytes 20 per cent. On February 19 roentgenogram of the chest showed coarse infiltration of both lower lobes with small confluent patches. The appearance was that of chronic inflammatory disease with a superimposed bronchopneumonia (Dr. Snow). On February 21 roentgenographic examination showed clouding of the right frontal ethmoidal sinuses and antrum. On March 5 there was noted a partial clearing of the lung in both lower lobes.

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† I am indebted to Dr. Emil Koffler and Dr. Alexander Goldman, The Bronx Hospital, for the privilege of studying cases 1 and 2, to Dr. Ephraim Bluestone, Dr. David Perla (Montefiore Hospital), Dr. K. M. Bowman (Bellevue Hospital), Dr. George Baehr and Dr. Paul Klemperer (Mt. Sinai Hospital) for the follow-up studies and pathological material in case 1. I also wish to acknowledge the kindness of Dr. Henry Greenberg for the clinical data from Fordham Hospital in case 2 and that of Dr. Benjamin F. Sandler and Dr. Joseph Ehrlich for making available the clinical and pathological material in case 3.

The temperature ranged from 99 to 102° F. for approximately one week after admission, following which it fell to normal. The patient was discharged on March 8, 1936 and re-admitted on April 27. Her asthma had continued unabated and the patient lost 18 lbs. in weight. The blood pressure on admission was 150 mm. systolic, 92 mm. diastolic. She was considerably more distressed and orthopneic than on her previous admission. Adrenalin administered intravenously provided considerably more relief than when given subcutaneously. The asthmatic paroxysms subsided somewhat. On May 21 the fundus examination revealed no disease changes. On May 26 the patient complained of precordial pain.

Laboratory examinations were as follows: Examination of eight specimens of urine revealed an occasional erythrocyte and trace of albumin, as had been previously found during her first admission. The blood counts were:

Date	Hgb.	RBC	WBC	PN	Eos.	SL	Misc.
4–27	82%	4,500,000	15,900	51	15	32	2
5–11	69%	4,100,000	25,200	85	1	6	8
5–25	79%	4,500,000	13,800	72		24	4

The blood calcium on May 4 was 11.1 and phosphorus 3.4 mg. per 100 c.c. Platelets on May 14 were 210,000 per cu. mm., bleeding time 1 minute 30 seconds, coagulation time 2 minutes, 30 seconds. Roentgenographic examination of the chest on May 2 suggested a chronic pneumonitis of both lower lobes. This was corroborated on May 13. On June 3 an electrocardiogram revealed a possible coronary occlusion.

Except for a temperature of 102° to 104° F. during the period from May 10 to May 15, the clinical course was practically afebrile. The pulse varied from 90 to 130. The patient was discharged on June 5, 1936, and re-admitted on August 22 with a complaint of loss of weight, weakness and wasting of both hands and abdominal pain. For three or four days before admission, diarrhea had been present. The patient appeared chronically ill and asthmatic. There was some weakness of the left upper extremity and tremor of the hands. Spastic intestine was felt in the left and right lower quadrants of the abdomen. The blood pressure was 120 mm. systolic, 80 mm. diastolic. Pulsations were present in the arteries of both upper and lower extremities. There was considerable atrophy of the muscles of the hand.

Laboratory examinations were as follows:

Blood counts:

Date	Hgb.	RBC	WBC	PN	Eos.	SL	Other Forms
8–24	80%	4,100,000	32,600	24	68	3	5
8–26			31,800	12	70	8	10
9–10			23,000	32	56	8	4
10–1	83%	4,400,000	22,200	34	52	10	4

Five urine examinations showed a trace of albumin in two specimens. Biopsy of the deltoid muscle revealed hyalinized striated muscle, but no evidence of periarteritis nodosa. Roentgenographic examination of the gall-bladder with dye failed to outline the organ. There was some enlargement of the liver. A barium enema study of the colon proved negative. The patient ran an afebrile course and was discharged on August 22.

Opportunities were afforded for repeated sigmoidoscopic studies at The Bronx Hospital and, after her discharge, at a nursing home and at the patient's residence. At the first examination the findings were unlike any picture previously encountered by us in any patient. In the rectosigmoid there were peculiar horizontal, linear, dark

FIG. 1. Intestine in case 1. Arrows point to focal and linear thromboses in the vessels of the mesentery. Note the segmental type of involvement and continuation of the lesions into the intramural branches of the intestinal wall (above upper arrow and to the left of lower arrow). Picture taken as a transparency (approximately × ½).

red streaks running in parallel lines, each approximately 1.5 cm. in length and separated by approximately 1 cm. of healthy mucosa. Direct pressure by a blunt instrument did not obliterate the streaks nor did gentle swabbing wipe them away. Careful examination with a telescopic device and green filter placed the lesion *within* a vessel since the latter could be seen proximal to each streak and, with great difficulty visualized as a thin almost bloodless hairline distal to it. Between the proximal and distal points the vessel appeared to be bellied out quite uniformly and the obvious inference was that it represented a thrombosed artery. Since there were no petechiae or other evidence of subacute bacterial endocarditis, an embolic phenomenon could be ruled out with reasonable certainty. Moreover, we had never seen this picture in cases of subacute bacterial endocarditis. Two follow-up examinations revealed a persistence of the lesions above described and, in addition, a definite elevation of the mucosa over the affected vessels. This indicated that they were located in the sub-

FIG. 2. Thickened, recanalized, healed vessel in the intestinal submucosa, case 1.

mucosa. Several small focal areas of thrombosis were also noted in the same as well as in previously unaffected vessels. Anatomically these corresponded to the end branchings of the sigmoid and superior hemorrhoidal branches of the inferior mesenteric and middle hemorrhoidal branches of the internal iliac arteries. In places the appearance was distinctly segmental. The clinical symptomatology indicated involvement of larger, extramural arteries inasmuch as the collateral circulation within the bowel wall was sufficient to maintain an adequate blood supply. No necrosis or inflammation of the mucosa was seen so that the persistent cramps could not be adequately explained on that basis. Previous experience had also shown that in arteriosclerosis the small intramural arteries presented a characteristic tortuous or corkscrew appearance and, in the later stages, straight tapering or obliterated vessels. Sections had revealed medial sclerosis and subintimal proliferation as the essential underlying pathology, but never thrombosis of the smaller intramural intestinal vessels. Correlated studies of the intestine in other cases of periarteritis nodosa in which the diagnosis had been proved at necropsy revealed lesions almost identical with those seen in our living patient and accordingly a diagnosis of periarteritis nodosa was made, probably stage 2 or 3 (inflammatory or granulation tissue stage) because of the high eosinophilia. In order to test the accuracy of these observations it was essential to

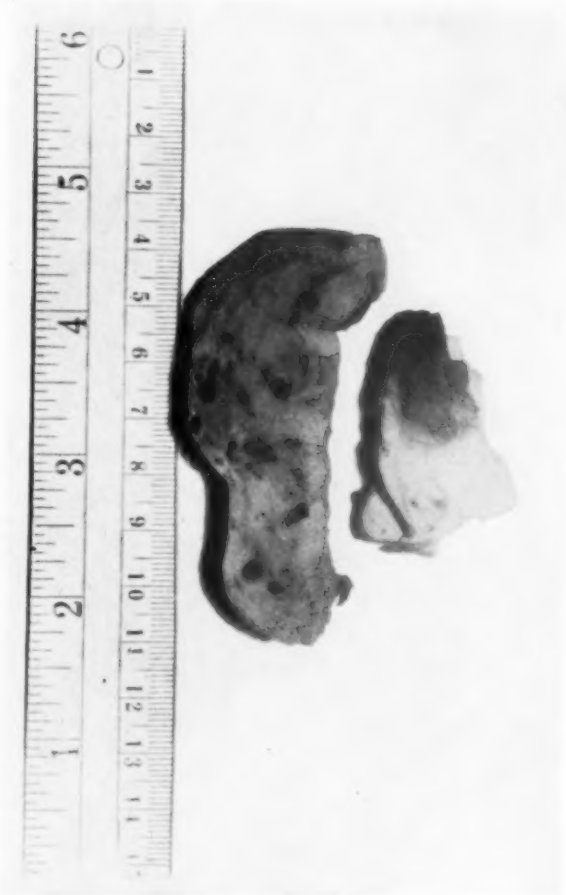

FIG. 3. Section of kidney in case 2, showing multiple thrombosed vessels with aneurysmal formation (specimen at left) and massive hemorrhagic infarction (specimen at right).

follow up the patient through each of the three hospitals where the subsequent clinical and pathological studies were carried out.

After a short stay at Montefiore Hospital the patient was transferred to the Psychiatric Division of Bellevue Hospital. Neurological examination revealed optic nerve atrophy and left wrist drop with sensory impairment. Spinal fluid examination was negative. The discharge diagnosis, three days after admission, was psychosis with somatic disease. The patient was then admitted to Mt. Sinai Hospital on December 21, 1936, with a diagnosis of periarteritis nodosa as previously made at The Bronx Hospital. Physical examination revealed a poorly developed, pale, cachectic middle-aged female who was irrational and disoriented. There was moderate cyanosis of the lips and finger nails. The neck veins were engorged and several small hard nodules the size of millet seeds were noted on the right side of the forehead. Several small lymph nodes were felt in the posterior triangles of the neck, axillary, epitrochlear and inguinal regions. There was some dullness at the right base of the lung with numerous moist and crackling râles. Râles were also heard at the left base and anterior aspect of the upper part of the right chest. The heart was slightly enlarged

FIG. 4. Mesenteric and intramural intestinal lesions in case 3. Note how in some of the focal mesenteric lesions the process appears to extend in a linear fashion (upper arrow). The typical intramural intestinal lesions, both focal and linear, are indicated by the two arrows at the right. Picture taken as a transparency (approximately normal size).

to the left; gallop rhythm was present and a pericardial systolic friction rub was heard at the lower left part of the sternum. The liver was smooth, tender to palpation and enlarged to a distance of two fingers'-breadth below the umbilicus. On the lateral aspect of the right knee there was noted a small cartilaginous-like movable nodule located in the subcutis. Another, somewhat softer, nodule was felt over the tenth dorsal vertebra. A small scar was seen in the left deltoid area (the site of a previous biopsy). There was slight edema of the ankles. Examination of the fundi revealed atrophy of the optic discs. The arteries were very narrow and a small hemorrhage was present above the right disc. Neurological study indicated median nerve paralysis involving the left hand with wrist drop. The interossei were wasted, the fingers being held in adduction with flexion of the proximal interphalangeal joints. The knee jerk was more active on the left than on the right side. Blood pressure was 150 mm. systolic, 110 mm. diastolic. The leukocytes were 19,250 per cu. mm., blood glucose 75 mg., urea nitrogen 75 mg. per 100 c.c. and carbon dioxide combining power 25 volumes per cent. The urine contained a trace of albumin and an occasional erythrocyte. The clinical course was rapidly downhill and the patient died on December 30, 1936, nine days after admission and approximately 16 months after the onset of illness.

The necropsy findings were as follows:

1. Periarteritis nodosa involving the vessels of the kidneys, liver, mesentery, diaphragm, spleen, lungs and heart.
2. Diffuse cortical scarring of both kidneys.
3. Subcapsular atrophy and chronic passive congestion of the liver.
4. Subacute suppurative pericarditis.
5. Hypertrophy and dilatation of the right auricle and ventricle.
6. Myocardial fibrosis.
7. Thrombosis of the left auricular appendage.
8. Generalized edema, ascites and bilateral hydrothorax.
9. Bronchopneumonia of all lobes.
10. Hemorrhagic infarct of the right lower lobe.
11. Marked pulmonary edema and congestion.

The causes of death were bronchopneumonia and cardiac failure.

Examination of the gross intestinal material borrowed for pathological study included only portions of the small intestine with attached mesentery. Marked involvement of the mesenteric vascular loops and straight vessels was present. There were nodular, linear and " skip " or segmental lesions. The latter were readily visible in the straight vessels coursing through the mesentery from the loops to the intestinal wall. The linear areas of involvement presented themselves as thickened vessels with parallel sides projecting slightly above the general surface level of the mesentery. The nodular lesions were focal and appeared to spread beyond the confines of the vessel wall. In some places the pathologic changes involved a loop as well as the proximal portions of the branches leading away from it. In others, there were small " spotty " focal lesions in the mesentery followed by a linear intramural lesion just after the vessel entered the intestine. Better areas for the demonstration of the lesions seen during life are shown in case 3. In the sections submitted with the gross material typical lesions of periarteritis nodosa were noted with thrombosis, infarction and acute necrotizing panarteritis. Many healed lesions were present in the intestine and kidney with

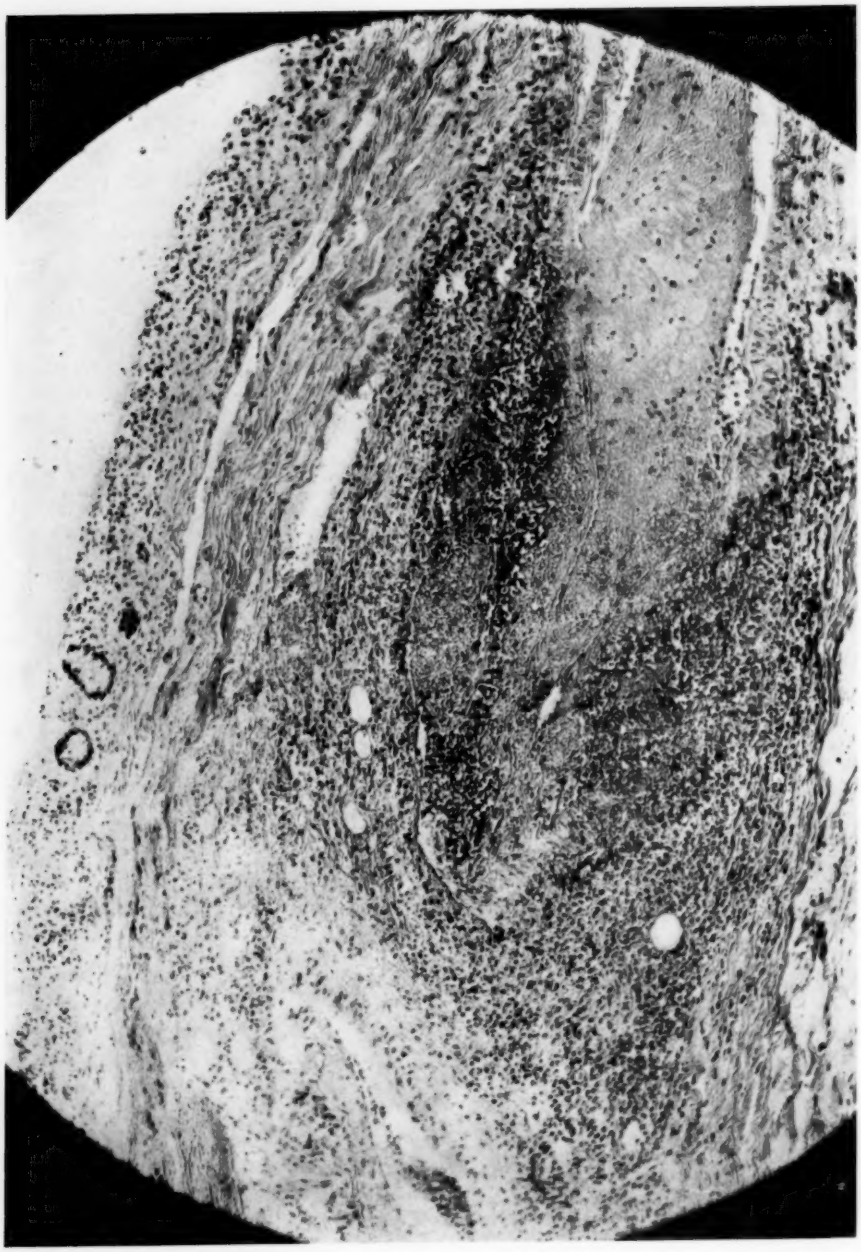

FIG. 5. Acute necrotizing panarteritis in a submucosal vessel which is thrombosed. Note intact mucosa.

recanalization and perivascular mantles of fibrosis and round cell infiltration. There was a recent massive hemorrhagic infarction of the myocardium. Various stages of the disease could be detected in different organs or even in different parts of the same section.

Case 2. L. A., female, aged 59 years, was admitted to Fordham Hospital on April 15, 1935, with a history of having had pain and a feeling of "pins and needles" in both feet for six weeks. Her feet felt cold and some relief was obtained by means of rest and the application of heat. Movement of the feet was painful. There was no evidence of vascular occlusion. Roentgenographic examination of the chest and both feet was negative. The blood chemistry and urine examination were normal. The blood pressure was 160 mm. systolic, 100 mm. diastolic. The blood count revealed nothing distinctive and the patient was discharged on April 20 with a diagnosis of arteriosclerosis of the deep vessels in the lower extremity.

One year later (April 23, 1936) the patient entered The Bronx Hospital complaining of coldness and heaviness in the lower extremities for six weeks and vomiting for five days. She stated that at the time of her previous hospitalization a skin rash and fever had been prominent symptoms. For the past few days the patient was unable to walk and suffered an attack of diarrhea and abdominal cramps lasting 24 hours. Physical examination revealed an aged woman, not acutely ill. The blood pressure was 180 mm. systolic, 104 mm. diastolic. The heart was enlarged to the left. There was a complete paralysis of the peronei of the left leg. The skin of both lower extremities had a mottled purplish discoloration which faded on pressure. Pulsations were felt in the vessels of both legs, but their elevation to a 45° angle did not produce blanching until one minute and it was not complete for another two minutes. There was impaired sensation to touch and pain on the inner and lower aspects of both legs. Knee jerks were present, but the left ankle jerk was absent. Neurological examination revealed involvement of the peripheral sensory fibers of the anterior tibial nerve and left foot drop. An indefinite mass was felt in the epigastrium. On April 28 the Rumpel-Leeds test was positive at the end of 15 minutes. On April 29 a painful tender mass which appeared to be an enlarged spleen was noted in the left upper quadrant of the abdomen. Repeated vomiting and abdominal cramps were present. The possibility of an acute surgical abdomen was considered with intraperitoneal hemorrhage due to a small rent in the spleen. A diagnosis of thrombosis of the splenic vein was made and on April 29 laparotomy (Dr. Wells) revealed a grapefruit-sized retroperitoneal mass in the left upper abdomen. The general shape resembled that of the kidney. The temperature ranged between 99° and 101° F. and pulse 80 to 120. The patient expired on April 30, twenty-four hours after operation.

The laboratory findings were as follows:

Blood counts:

Date	Hgb.	RBC	WBC	PN	SL	Bd	Other Forms
4–23	53%	3,300,000	26,100	86	11	0	3
4–27	56%	3,300,000	33,500	77	19	2	2
4–29	34%	2,000,000	35,000	73	10	9	8

No eosinophiles were seen.

On April 24 the reticulocytes were 0.2 per cent and platelets 240,000 per cu. mm. On April 26 the sedimentation rate was 18 mm. in 16 minutes. The Wassermann reaction was negative. The icteric index was 8.4, Van den Bergh direct delayed and indirect 0.7 units per 100 c.c. Gastric analysis showed a free acid of 6.5 and total

FIG. 5. Acute necrotizing panarteritis in a submucosal vessel which is thrombosed. Note intact mucosa.

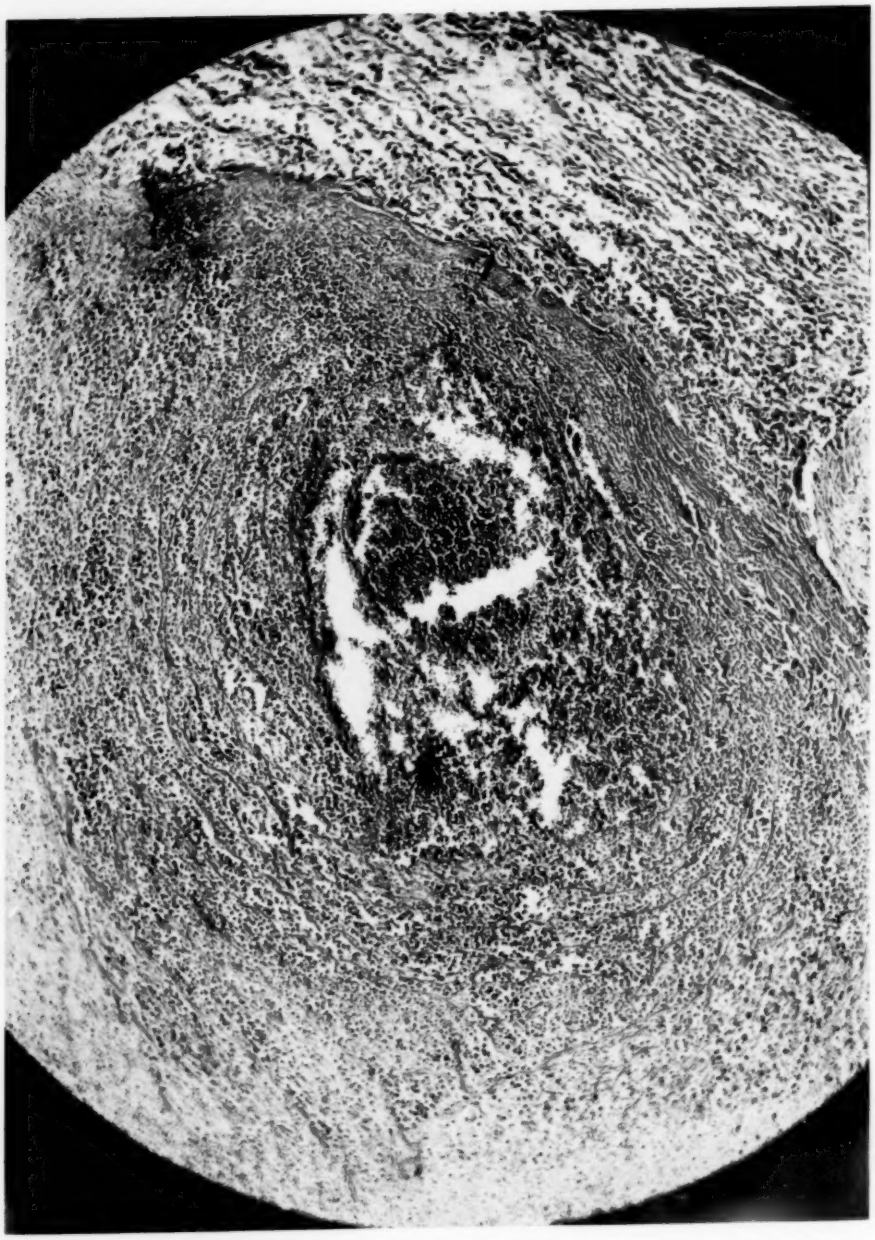

FIG. 6. Acute exudative type of inflammation involving all coats of the artery with edema, cellular infiltration, necrosis and thrombosis.

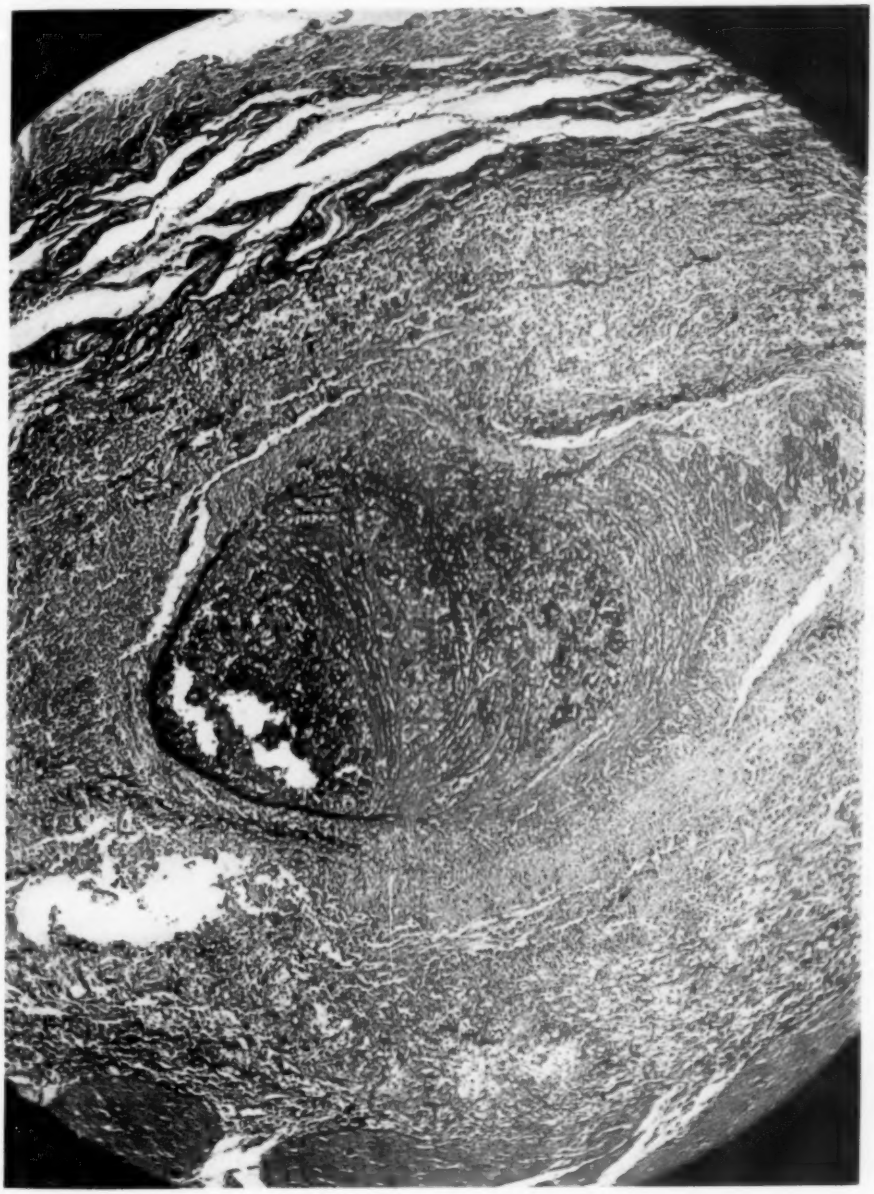

FIG. 7. Partially healed vessel with perinodular fibrosis, organization of the thrombus by fibroblasts and beginning recanalization. Note nodule at right and intact elastica at left.

acid of 25. On April 27 a Mosenthal test indicated a tendency to fixation of specific gravity between 1.014 and 1.016. The urine contained albumin and granular casts on one occasion. The blood urea, glucose, uric acid and creatinine were normal.

Cut section of the gross kidney specimen revealed the characteristic lesions of periarteritis nodosa with massive infarction of renal tissue. Small and large thrombosed vessels were clearly visible to the naked eye with perinodular or aneurysmal formation and hemorrhage. The histopathology revealed changes varying from medial and subintimal necrosis to complete disintegration of the wall with rupture and hemorrhage into the adjacent parenchyma. The vessel wall was thickened, edematous and the fibers separated by inflammatory cells chiefly of the polymorphonuclear neutrophilic, eosinophilic, lymphocytic and plasma cell varieties. In some, fibrosis had already replaced the periarterial nodule and organization and recanalization of the thrombi were seen.

Case 3. Since the general aspects of this case have been reported by Sandler,[2] only the intestinal material borrowed for study will be presented. The patient was a white male, aged 54 years, and the total duration of illness was approximately one year. The outstanding clinical features were multiple skin nodules, muscle spasms and weakness, abdominal pain and a left hemiparesis. The blood examinations revealed a secondary anemia, a leukocytosis of 21,000 with 55 per cent eosinophiles. About two months later the leukocytes fell to 14,000 and only an occasional eosinophile was noted. A clinical diagnosis of periarteritis nodosa was made (Dr. Sandler) and at necropsy characteristic vascular lesions were found in the heart, lung, liver, spleen, kidney, gall-bladder, testis and intestine (Dr. Ehrlich).

Upon examination of the intestine obtained at necropsy there were seen two types of gross lesion, viz.: nodular and linear. When viewed as a transparency, the nodular lesions stood out as oval, localized, hemorrhagic protrusions of the vessel wall from which the delicate proximal mesenteric branch emerged rather abruptly. In some instances it appeared as though there was a tendency for the process to extend slightly beyond the confines of the nodular lesion along the course of the vessel. The linear lesions involved the vessel in a uniform and longitudinal fashion, standing out as rigid, dark red thrombosed cords which elevated the tissue above it. The intramural vascular lesions were clearly visible through the intestinal mucosa which was slightly raised. The general direction was transverse corresponding to the manner in which the vessels normally encircled the intestinal wall. A rather striking feature was the " skip " or segmental nature of the vascular lesions, linear or nodular thrombosed areas alternating with apparently normal portions of the vessel. Often this could be traced in the mesenteric and intramural branches of the same artery. Microscopic sections revealed an intact mucosa with acute necrotizing panarteritis of the small submucosal arteries. The close proximity of these branches to the mucosa accounted for their easy visualization in the gross specimen. Thrombosis, necrosis of the wall with partial destruction of elastica, periarterial nodule and aneurysmal formation with rupture and perivascular hemorrhage were the essential histopathological features. In some sections partial organization of the thrombus was taking place by young fibroblasts and there appeared to be some recanalization. Considerable vascular and perivascular infiltration by polymorphonuclear leukocytes and mononuclear cells was evident in vessels which were still intact.

Discussion

Perusal of the data presented in these cases reveals the presence of the characteristic diagnostic tetrad of Meyer and Brinkman in each instance, viz.: chlorotic marasmus, abdominal manifestations, nephritis and polyneuritis, polymyositis. In each of two cases (1 and 3) there was a high eosinophilia, a finding common to relatively few diseases, one of them being periarteritis nodosa. Its absence does not exclude the disease (e.g. case 2) since, according to Arkin,[3] marked eosinophilia is encountered chiefly in stage 2 or 3 (acute inflammatory or granulation tissue stage), being negligible or absent in stages 1 and 4 (degenerative and healed stages respectively). In cases 1 and 3 the eosinophilia, present at the height of the acute phase, disappeared several months before death.

The essential pathological features of periarteritis nodosa consist of a necrotizing panarteritis affecting chiefly the vessels of the kidney, heart, gastrointestinal tract, mesentery, liver, muscles, cranial and peripheral nerves in approximate order of frequency. The noxious agent enters the vessel wall either directly from the lumen or through the vasa vasorum of larger vessels (Arkin). There is produced an exudative type of inflammation in the media with edema, fibrin deposition, coagulation necrosis, cloudy swelling and hyaline degeneration of the muscle fibers. Similar subintimal changes may occur in the smaller arteries with almost complete obliteration of the vessel lumen. There is a diffuse cellular infiltration of the entire wall by plasma cells, lymphocytes and polymorphonuclear cells chiefly of the eosinophilic type. Microscopic involvement of the wall is generally linear. The fibrinous and cellular exudate extends to the intima and adventitia, the elastica becomes fragmented and thrombosis occurs; in other instances necrosis of the media with subsequent weakening of the wall is followed by aneurysm-like formation and rupture into the surrounding tissue. The process as described comprises stages 1 and 2 or degenerative and acute inflammatory stages, respectively. These and the other two blend imperceptibly with one another or more than one stage may be present in different vessels simultaneously. The acute inflammatory stage is followed by a proliferative or granulation tissue stage (stage 3) in which fibroblasts and thin walled blood vessels grow into the damaged areas producing subendothelial thickening or even invading the thrombus within the lumen. Recanalization may occur or complete occlusion of the vessel. The same reparative process occurs in the media and adventitia, an area of proliferative fibrosis replacing these layers and often the zone of perivascular aneurysmal or nodular formation. Sometimes a linear mantle of periarterial fibrosis without nodule formation is seen, particularly where the lesions are linear in the first place (stage 4 or healed stage).

The etiologic agent of periarteritis nodosa has not been definitely established. In general, there are three schools of thought, viz.: (1) Specific virus (Arkin, Haining and Kimball); (2) rheumatic (Ophuls, v. Glahn and

Pappenheimer, Friedberg and Gross); (3) post-infective mesarteritis (Spiro, Gruber).

According to Arkin, clinical diagnosis is possible only in stages 2 and 3. Infarction, atrophy or scarring of the organs supplied by affected vessels may offer an indirect clue, but the real underlying pathology is generally not ascertained during life. Wever and Perry [4] reported a case of fatal perirenal hemorrhage in which the condition was deemed surgical very much like case 2 with renal infarction reported above. Fever is present during the active stages (1 to 3) and absent in stage 4, according to Arkin. Focal lesions in various organs are common, but difficult to interpret even in the presence of a leukocytosis as seen in stage 2. Coronary or renal involvement is relatively frequent, but more common causes than periarteritis nodosa are generally suspected. Involvement of the extra- or intramural intestinal vessels appears to be much more frequent than retinal involvement and offers a promising field for non-operative clinical diagnosis since visualization of the intramural branches was actually effected in our patient. Arkin has even described a rather picturesque involvement of the mesenteric vessels (as seen at necropsy) in which hempseed-like nodules studded the vessels like a string of pearls (perlschnurartig). The intramural "skip" or segmental involvement which we noted at sigmoidoscopy is probably part of a similar picture. Intestinal symptoms and signs consist chiefly of cramps and diarrhea which appear to be due to involvement of the larger extramural branches with subsequent anoxemia of the part of the intestine supplied. Thrombosis of the principal mesenteric arteries with intestinal infarction is uncommon. Involvement of the smaller intramural branches alone is rarely extensive enough to produce anoxemia as their rich arborizations are sufficient to maintain an adequate blood supply. No broad assumptions can be made on the basis of our limited experience, but in view of the fact that intestinal lesions are so common in periarteritis nodosa, their detection at sigmoidoscopy may prove to be a useful diagnostic procedure in this disease.

Summary

Correlated clinical and pathological studies have been presented in a case of periarteritis nodosa diagnosed during life by sigmoidoscopy.

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SOME PROBLEMS CONFRONTING THE PHYSICIAN IN THE EXAMINATION OF AUTOMOBILE DRIVERS *

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The history of medicine has demonstrated over and over again the alertness of the physician to meet new problems. When firearms were introduced into the art of warfare surgeons rapidly learned new technics of saving life. With an increased use of machinery in industry, industrial medicine and surgery have shown a parallel development. But strangely enough, in dealing with the medical aspects of the traffic problem, there is a detectable lag.

The real problems set up by the existence of the motor car have not been apparent until the last 15 years. Surgery has met the particular emergency set up by the motor car because of the fact that surgical technic can be adapted to various purposes and because injury due to violence in its essentials is very much the same whether caused by a motor car or by an axe or a club. The problem of medicine in the consideration of the damage done by motor cars is somewhat different. The medical man is asked to take part in the solution of this problem from two angles.

The first is the problem of what part the physical or mental condition of the patient may have played in causing the accident and in determining the patient's responsibility for it, and what important medical changes have occurred to the patient or others as the result of an accident. This last consideration, I think, is more important in a civil case than in a criminal one. It is sufficient, in the criminal court, to show that damage was done to the victim; the amount of damage must be assessed in the civil court.

The second problem, and the greater one, is to determine who should drive. Here the fields of preventive medicine, general medicine, and law overlap. The matter is important from the standpoint of preventive medicine because public health demands that the mortality and morbidity due to automobile accidents be curbed. When we consider that two years ago 40,000 people were killed in the United States from this cause alone, the problem cannot be ignored. Even last year (1939), which was considered a fair year, there were still about 32,000 people killed and 1,200,000 injured throughout the country.† It is not the public health worker, however, who

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† From: Smash Hits of the Year, The Travelers 1940 Book of Street and Highway Accident Data, Hartford, Connecticut, The Travelers Insurance Company, 1940, page 3.

can make the examination or do the research to determine what constitutes a satisfactory physical condition in one who wishes to operate a motor car.

One aspect of this problem lies in the question of whether the criteria and standards set up by various consultants, including physicians at the request of license bureaus and other law enforcement agencies, can be sustained in a court of law. It is easy enough to set up hypothetical standards, but it remains a matter deserving of considerable thought to determine whether there is definite evidence of the validity of these standards which can be laid before the judge in an honest and convincing manner.

The problem of medical standards for safe drivers is one in which few medical men can qualify as real experts inasmuch as very little research has been done outside of that which we have done in the Psychopathic Clinic of the Recorder's Court in Detroit.[1, 2] When the Clinic was set up in October of 1936, as a joint project sponsored by the Judges of the Traffic Division of the Recorder's Court and the Judges of the Recorder's Court, the personnel of the Clinic canvassed the literature to see what definite information there might be on the subject of personal driving standards. A resolution presented by the Section on Ophthalmology, coördinated with one from the Committee on Physical Standards for Drivers of Motor Vehicles, was adopted by the House of Delegates of the American Medical Association, setting forth quite reasonable standards.[3] New standards were set up in 1938 but they are still open to severe criticism.[4] In spite of the fact that certain rather gross examination standards have been set up in the driving laws of some states, the physician remains at loose ends. Most medico-legal terms have not been adequately defined as regards psychiatry and, perhaps, as regards medicine in general, but the standards, grossly, are that, in various states, the following are disqualified: habitual drunkards or drug addicts (25 states); insane or feebleminded (18 states); idiots, imbeciles or epileptics (17 states); persons having physical or mental defects causing lack of reasonable driving control (22 states); persons adjudged afflicted with a mental disability or disease (7 states). There are also states where the deprivation of license is mandatory when certain of the above conditions are present.[5]

However, from the point of view of utilizing these laws so that they will be most valuable to the driving public much remains in question. For example: Shall imbecility be determined by a clinical definition or by virtue of a dead-level intelligence quotient? Do enough persons afflicted with petit mal know that they are suffering from epilepsy so that they can be made to report under these laws? Does hystero-epilepsy, a functional disease, fall under the gross head of epilepsy in dealing with traffic problems?

These and many other questions arise in the administration of the medical problems of traffic. Standards for these are, therefore, in a confused state. Visual defect standards are based on those urged by the National Safety Council and defined by the Ophthalmology Section of the American Medical Association. Those of crippling are merely whatever the examiner and the

Police Department wish to call severe crippling as determined by the way the man can operate a motor car on a road test. In the Clinic we have seen many sufferers from infantile paralysis, all of whom could operate a motor car well enough to pass a driving test, but who in a sudden emergency were unable to react quickly enough to bring their withered limb into action with sufficient strength to keep from having an accident. There is no question but that with special apparatus and in certain special cases the sufferer from infantile paralysis is a safe driver, as determined by a road test, but the standards themselves remain to be established. Perhaps all-inclusive standards will be too difficult to develop and each case will need to be evaluated on its merits.

The first consideration for the physician is his obligation to give competent advice to the Court in determining how culpable an individual involved in a traffic accident might have been.[6] There have been a number of persons brought into the Recorder's Court Traffic and Ordinance Division who have maintained that they were ill and, therefore, not responsible for the accident in which they were involved. As a general rule, the Judges of the Recorder's Court Traffic Division have referred such cases to the Clinic for an evaluation. This is not because they doubted the reliability of the physician who had given a certificate which stated that the man was not in good physical condition, but because it does, in their opinion, require a special ability to evaluate how important these physical disabilities were in the specific situation. The testimony of the physician in Court regarding a man's condition, and its evaluation in the sense of indicating responsibility or lack of responsibility for an accident, requires a knowledge of the special capacities needed for operating a motor car. There is, however, no difference in the need for special training between the physician who is willing to give a certificate to enable a patient to escape the consequences of his act and the physician who is able to make special examinations for the purpose of recommending whether a man should or should not have a license.

In general, then, there are three considerations which cannot be overlooked in evaluating a person's physical condition to decide whether he was responsible at the time of committing an offense or having an accident, or whether he is physically able to drive a car. There are a number of traditions and facts on the subject, but in general we might say that these three conditions are: first, an adequate mentality; second, an adequate physical condition, including, of course, an intact central nervous system; and, third, adequate vision, which is tied up, of course, with both the first and second considerations.[2]

For the time being I shall mention the psychiatric side only very briefly. It is sufficient for the physician to know that the psychiatric side cannot be ignored. Many a man whose physical condition is such that one would consider him unfit to drive might very well be permitted to drive because of his intelligence, his favorable attitude, his knowledge of his weaknesses, and a

desire to compensate, which he can do by not driving on slippery days and nights or in heavy traffic.

The Clinic has seen many color-blind individuals who have proved to be so by the test, but who were not to their own knowledge actually color-blind. They had never had any difficulty in distinguishing between the red and the green lights, and until we pointed out to them that on the Ishihara test they were unable to distinguish between red and green letters and numerals, the fact that they were color-blind was entirely unknown to them. Most of these cases (and we found about 4 per cent of our cases to be partially or completely color-blind) are able to drive cars and to keep out of trouble. They were not referred to the Clinic because of their color-blindness. They were usually referred because of some other weakness that had been brought to the attention of the Court. All but three of these cases were able to tell the difference between the red and green lights and this was not due to the position of the lights on the standards, because in our Clinic we move these lenses around. The worst color-blind cases were two seriously feebleminded individuals who had got into a great deal of trouble. Their offenses had not been numerous, but were quite serious. In one case the man had actually gone through a red light against traffic, seemed to be quite bewildered by the fact that traffic was going in the opposite direction, and was unable to compensate for his color-blindness because of his feeblemindedness.

In evaluating the importance of physical ailments in the driver, his mental condition must not be ignored. If the physician is examining a man because he wants to get out of the consequences of his violation, or because he has been refused a license and wants his physician to speak to the License Appeal Board in his behalf, the physician would do well to note a few important psychiatric considerations.[7, 8] The first one is: What is the patient's attitude? Does he have a feeling that the driving privilege is one which is given to him by the Constitution or by God, and that nobody has the right to take it away from him? If he explains any accidents or difficulties in which he has been involved, does he always take the attitude that it is the other man's fault, that he could not possibly have been at fault? If this is the case, it would pay one to be very suspicious. It is undoubtedly true that many people have accidents for which they are not to blame, but it has been my experience, after seeing almost 800 cases of this sort, that even the allegedly innocent party contributes in some measure to an accident.

The attitude taken by most modern traffic courts in this connection is that if a man is not able to stop in time, even if he has the right-of-way, he is almost as much at fault as the offender who drove across the right-of-way, making it necessary for the victim to stop. The good driver, the one who is not violating the traffic laws, is able to stop in time to avoid an accident. However, it must be admitted that there are situations which arise where the conditions are so misleading (such as a blind corner or other trap which is improperly marked) that although the man may be taking due care, he does get into trouble. In these days, in view of the thousands of dollars

being spent on markers, signs, and other indicators to prevent an individual's going too fast in a dangerous place, it is rather a doubtful excuse for the defendant to say that the emergency arose so quickly that he could not react in time.

If an individual, who is to appear before a License Appeal Board or similar examining body for a hearing to determine whether he should have a license, wishes to bring with him a doctor's certificate, it would be well for the doctor who examines him to make an investigation as to any signs and symptoms of psychosis. There are very definitely a number of insane individuals driving who show a suggestion of a paranoid picture or in whom the neurological examination indicates faint signs of central nervous system syphilis, and the doctor may be jeopardizing his reputation by giving a man of this sort a certificate so that he will be granted a driver's license.

To evaluate the general physical condition of the driver does not require any unusual technic. Any competent physician can recognize signs of arteriosclerosis, nephritis, systemic disease, and metabolic disease in these days. Even rather early cases are detectable clinically, although occasionally it is true that the laboratory must be brought in to assist. Just how sick a man must be before he should not drive is a problem which has not yet been adequately studied. I do not know of any really good standards. In certain foreign countries the rule is that if there is any degree of illness at all, the man should not be permitted to drive.[9] If such a broad ruling is invoked, the diabetics, the mild arteriosclerotics, the mild sufferers from poliomyelitis, and the mild nephritics are handicapped and are unable to go about their business when quite possibly they are safe drivers.

A number of reporters in Europe admit that the too strict attitude should be revised, and it is becoming the duty of clinics such as ours in Detroit to establish new standards. We will require the help of the medical profession in doing this. Sooner or later we will have to circularize physicians and find out from them which cases have had accidents and which have not. But the time does not appear to be ripe.

Nevertheless, I shall present a few experiences, and some opinions about physical disorders which we feel to be justified. We have had a large number of arteriosclerotics coming through our Clinic. We have had 15 cases where the blood pressure was over 160; in half of these cases there had been an accident. In none of them was the accident serious nor was there a death, so that we might say that the mere presence of high blood pressure should not make it necessary to take away a man's driving privileges. However, if there is any danger of syncope—and this must probably be left for decision to the doctor's own experience—a man suffering from hypertension of any sort might well be advised not to drive. If he has never had a syncopal attack, if his blood pressure seldom goes over 180, careful observation of his conduct and evaluation of his subjective syndromes might make it possible to state that he was competent to drive. I would be skeptical about serious cases, but I would not like to lay down any hard and fast rule.

We have seen a few diabetics. Most of them did not come to our attention because of their symptoms, for usually they had already been placed under treatment. In one case, that of a feebleminded Negro who was taking insulin, the man decided after taking his noon-day injection that he would go for a drive before he had his lunch. The subsequent accident, which resulted in injury to nobody but which badly battered several cars, was probably due more to his feeblemindedness than to the condition of his blood sugar. I have checked with several physicians who have large diabetic practices, and it is their opinion that diabetes per se, particularly the milder or well controlled forms, is not a contra-indication to driving. However, it is well for a patient who is taking insulin to be warned that he must not drive his car until he has eaten an adequate meal after the injection. Of course, any intelligent diabetic will carry with him a supply of readily available carbohydrates. We have been promised by the Detroit Diabetic Association that it will make a survey for us to determine whether there is any accident tendency among the patients under their observation. I very much doubt whether such a tendency exists.

Cardiacs are very serious problems because we have in the accident reports a number of casualties where a man known to have heart attacks has lost consciousness or has died suddenly at the wheel. Any man with severe syphilitic aortitis or an active endocarditis certainly should not drive. The arteriosclerotic heart, many instances of which have been seen in the Clinic, does not seem to have interfered with the patient's driving ability, particularly in its milder forms. Nevertheless, if the patient has had a history of decompensation, he should be warned that he must not drive if he has any dyspnea or other signs of beginning decompensation, and if he is to keep his license, he should be checked rather frequently by his physician. He need not necessarily be deprived of his license, but it should be limited. Some day perhaps we will have to have endorsements on these licenses to indicate that the periodic examination is being carried out. The expense and hardship of such periodic examinations probably would be much less than the expense and hardships the man would have to undergo were he unnecessarily to be deprived of his driving privilege. By the time a man has severe arteriosclerotic heart disease it is quite possible that he will have other weaknesses, particularly in reaction time, in the nervous system, or in vision, which would make him a risk on the highway.

These are the chief systemic diseases which have been brought to our attention. We are making a special study of neurological disorders, particularly of sufferers from infantile paralysis of whom there are many, and it has been the opinion of the local licensing authorities that if such cases can operate a car to the satisfaction of the examiners of the State Police, they should be permitted to drive. We have had some of them referred to the Clinic because of minor accidents, and the cases have had to be evaluated on the type and degree of disability. For instance, the last case we saw, a young man 18 years of age who had only had about three weeks' driving

experience, had completely paralyzed lower extremities on both sides and a partially paralyzed right arm. Now, this man could not adequately handle the pedals of his car even though he kept his feet upon them and pushed his knees down manually to depress them. Because of this, he ran into the back of a truck, did not do much harm, but revealed to us and to the Court that he was a greater risk on the highway than the normal individual, and that the chances were high that he would never be a safe driver. We always feel very sorry for these individuals, and a good deal of pressure has been brought to bear upon us to be lenient with them for economic reasons. We can never see why an individual's economic life should be held superior to the life of a victim.

There is no question that the eye findings in the case of license candidates, or in one who is trying to escape the consequences of his traffic misdeed, are important, but just what should be considered significant and what the standards should be, I do not think have properly been determined as yet. I mentioned above the fact that color-blindness, which is supposed to be very important in traffic, has been, in our experience, of rather small significance. Color-blindness and limited fields of vision are stressed by some psychologists and by amateurs in the field of physical and mental examinations of traffic offenders, but, out of 760 cases, we found only eight with marked diminution of the field and these were obviously suffering from diffuse neurological diseases, and their inability to drive was so obvious that they were never granted licenses.

Paretics, of course, have limited fields of vision, but their symptoms can be detected through the usual neuropsychiatric examination.

Visual acuity standards have been set up by the Section on Ophthalmology of the American Medical Association, but these standards have, in my experiences, worked some injustices because of over-strict application by lay eye-testers. In many cases the competent ophthalmologist can set aside these standards without permitting a dangerous driver to be at large on the highway.[10, 11]

The Clinic has seen several cases where the vision in both eyes has been as low as 20/200, yet the individuals have never been in any trouble. One of them, referred for research purposes, was a truck driver with over 500,000 miles of driving experience, who was found to have a very low visual acuity. Nevertheless, his route was distinctly channelized; he followed the same streets day in and day out; he drove rather slowly, was very alert, very cautious, and very anxious to maintain a good record; his poor vision was not a handicap, and we do not expect to find him in the Clinic unless he deteriorates.

There are a number of other functions of vision which are partly psychological, such as depth perception, judgment of speed and distances, and judgment of spatial relationships.[12, 13] These all require special apparatus for their proper testing, and the average physician would not find it worthwhile to have this equipment. If the physician is doubtful about a man's vision,

it would be well for him to call in a consultant or, if it is possible, as in Detroit, to refer the man to a Clinic, such as ours, so that he might be given a certain amount of specialized advice about his patient's eye condition.[14]

The help of the physician has been asked in numerous cases involving intoxication while operating a motor vehicle. Physicians are sometimes asked to testify in Court that the individual facing a charge of drunken driving was really sick at the time of his accident or arrest and that alcohol was only secondary. Occasionally the physician is asked to state under oath that the patient was not drinking at all and that the appearance of alcoholism was the result of the use of drugs, of family trouble which resulted in "nervousness," of fatigue, or of some other cause. The experience of the Clinic leads one to believe that upon occasion the ends of justice are decidedly served by the testimony of the medical expert in such cases. Certainly, for instance, a man should not be sentenced for drunken driving if he had not been drinking but had suffered a cardiac attack which caused him to stagger and faint. Nevertheless, the physician who testifies in such cases has not done his whole duty, particularly if he is the family doctor, if he does not follow up the circumstances surrounding the traffic violation or accident. If the patient is subject to convulsive attacks, his physician should warn him not to drive. It would certainly not be unethical for a physician to urge the man to surrender his license.

The greatest circumspection should be used in testifying in cases involving drunkenness. Physicians have been made dupes by casual acquaintances, and by patients who have been drinking and whose drinking, while it might perhaps not have been the critical factor, was definitely a contributing factor in the accident. Physicians must not forget that even small doses of alcohol administered to certain physically and mentally weak cases will make them dangerous on the highway, whereas they might not be from their physical ailments alone. Syphilis is an example of such a situation. We have on record the case of a sufferer from syphilis evidencing very mild central nervous system manifestations who normally was qualified to operate a car but who, after having only a little beer, was subject to convulsions.

Although the Committee to Study Problems of Motor Vehicle Accidents of the American Medical Association has set up standards for the amount of alcohol in the blood which constitutes drunkenness, the value of these standards is open to question.[15] The amount of alcohol concentration resulting in drunkenness is now set at .15 per cent by weight. This is probably too high to include the majority of dangerously drunken drivers. Certainly an individual who has that much alcohol in his blood is not a good risk on the highway and should be sentenced as a drunken driver; but the majority of individuals who absorb that much alcohol are really incapable of sitting behind the wheel of a motor vehicle and operating it, and consequently "pass out" before they try driving. We seldom see individuals as intoxicated as this arrested for drunken driving; in fact, a truthful history of "a few beers" taken on an empty stomach is the usual one.

The physician who knows a chronic alcoholic of this sort would do well to prevent his driving a car, for the probabilities are that, if he gets into trouble even though it is due to no fault of his own, he will be sentenced as a drunken driver and, in most states and cities, especially in Detroit, he will be given the most severe penalty the judges can devise.

It is not to be expected that the physician in private practice will have apparatus for testing the breath, urine or blood, and it is open to serious doubt among lawyers whether such tests might violate the patient's constitutional rights if he were compelled to submit to them. Since in many cases the tests are administered by a layman (police officer), their validity will for a long time be open to question. If such tests are to be given, it would be well for physicians to acquaint themselves with the intricacies of their chemistry so as to qualify as experts in this respect when called upon to testify in drunken driving cases.

In conclusion, I should like to cite a case. A 63 year old man was sent to the Clinic by one of our traffic judges. His blood pressure was only 140 mm. mercury systolic and 80 mm. diastolic, but his vessels were tortuous, and we could feel in the arms definite indication of thickening of the walls, almost to the degree of a pipestem vessel. His judgment of speed and distance, his reaction time, and his depth perception were poor. On the intelligence test he rated only an intelligence quotient of 70, which was about that of a nine-year-old child. This might not be bad in a younger man, but was probably an indication of deterioration in his case because in the past he had been a rather good salesman. He was over-talkative, silly, and showed signs of beginning arteriosclerotic psychosis. We examined him thoroughly, gave him all sorts of physical examinations, urinalysis, serology, tested his eyes by every possible means, and came to the conclusion that he was not a safe driver on the highway. We might note, too, that he had received over 150 tickets for minor traffic offenses. He had settled these with impunity at the Violations Bureau. When he was brought before the Judge, he talked in such a foolish fashion that the Judge sent him to us. He told the Judge that he had committed his last violation in order to come up and talk to him. After we recommended the revocation of this man's license, our recommendation was followed up by the Judge and the Secretary of State's office. The man immediately set in motion the procedure to get his driver's license back. Merely on his record we would have thought that his application would have been rejected, but our report was requested and transmitted to the Appeal Board, and on the basis of it he was turned down. When he was rejected this time, he went to a local neuropsychiatrist, and told him that he had been unfairly treated at the Clinic. This physician examined him, gave him a neurological examination but without doing any psychiatric inventory, did not notice the tortuous vessels apparently and, of course, not having the special apparatus for testing his eyesight, thought that even though the visual acuity was inferior, the man had adequate vision. The doctor wrote a letter to this effect to the Appeal Board which still withheld the man's license. The

patient's lawyer then said that he would take the case to the Circuit Court (the tribunal hearing such appeals), if the man would pay enough money. The petitioner tried to get the doctor's certificate for the lawyer, but in the interim the physician had communicated with us and been informed of our findings, so that he realized that the man had made improper use of his services, and, therefore, refused to issue another certificate. The petitioner then secured another lawyer who took the case to the Circuit Court and subpoenaed one of the best surgeons in town to testify concerning the petitioner's ability to drive a car. This surgeon testified on the stand that he found no arteriosclerosis, and that the man's eyesight was good, but when asked what the man's mental condition was, he said he was not a psychiatrist, probably because he realized from the petitioner's conduct when he was on the stand that there must be something the matter with his patient's mentality. Both of these doctors would have been well forewarned had they talked the matter over with us in the Clinic, or had they made a special study of the traffic situation with special reference to its medical aspects.

Naturally, the Clinic has no axe to grind. It is impartial, having a desire only to protect the driver from his own folly, and to protect the public from a dangerous driver. Often cases who are handicapped and who would make a poor impression before a Jury are warned that although legally they can have a license, if they get into an accident the Jury would consider it to be their fault. As a general rule, it has been our experience that the doctor is foolish who advises a traffic court that a man is in poor physical condition and, therefore, is not responsible for his accident. This almost immediately means revocation of the license, unless the doctor has looked into the situation so thoroughly as to be able to prove that the occurrence was one which would not repeat itself during his patient's driving career. Of course, if the doctor is sure that the accident is an isolated incident, and that the syncope or other cause of an accident will not recur, he should not hesitate to state this to the Court (his patient is certainly entitled to such service), but the physician would do well to lean backward before sending such a patient back on the highway.

To conclude, then, it must be obvious that there is a very definite place for the physician in dealing with this traffic problem to aid cases to get justice either in the Courts or when trying to get a license, but very special considerations should enter the physician's mind before he puts himself on record in regard to the patient's condition in relation to his ability to drive a motor car.

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CLINICAL STUDIES WITH THE AID OF RADIO-PHOSPHORUS. III. THE ABSORPTION AND DISTRIBUTION OF RADIO-PHOSPHORUS IN THE BLOOD OF, ITS EXCRETION BY, AND ITS THERAPEUTIC EFFECT ON, PATIENTS WITH POLYCYTHEMIA *

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The purpose of this paper is (*a*) to indicate the amount of radio-phosphorus (P^{32}) retained by various fractions of blood of four normal individuals and six patients with polycythemia; (*b*) to indicate the amount of P^{32} excreted in the urine and feces of the normal individuals and some of the patients; and (*c*) to present the hematological and clinical findings of the patients before and after the administration of P^{32}.[1]

Materials and Methods

The radioactive phosphorus was produced by the Berkeley Cyclotron.[2] The four normal individuals were robust, ambulatory workmen with recently healed fractures, all of whom had received the same type and quantity of food for a period of from one to eight weeks, and each of whom had a single regular bowel movement daily during the same period, previous to the administration of P^{32}. It was impossible to control the diets or time of excretion of the patients. The blood withdrawn from veins was heparinized, cooled and centrifuged exactly 20 minutes at 1450 times gravity to insure constant volume. The buffy coat was aspirated, suspended in equal amounts of heparinized Ringer's solution and centrifuged exactly 20 minutes at 1450 times gravity. The plasma was then removed from the original tube and finally the red blood cells. The stroma of the red blood cells and the phospholipid, acid soluble and nucleoprotein fractions of red and white blood cells and plasma were obtained by technics previously described.[3, 4, 5, 6] The various blood samples and excreta of the patients and normal individuals were ashed at 400° C. in appropriate crucibles, and assayed for radioactivity by use of an electrometer. All the determinations of P^{32} recorded in the tables and graphs were corrected for decay to the date of administration.‡ One microcurie (μc) or 1/1000 millicurie (Mc) is equal to 37,000 beta particles per second.

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‡ The half-life of P^{32} is 14.3 days.

Results: In table 1 are listed the four normal individuals and the six patients with their complaints and physical and laboratory findings before the initial administration of radio-phosphorus and the hematological changes and clinical results 7 to 15 months after the initial administration. In general the hemoglobin, red blood cell and white blood cell levels of the patients eventually reached near normal levels after various amounts of radio-phosphorus. There was marked clinical improvement and marked improvement in the physical findings in all of the patients during the period in which they were studied.

The average percentage of the dose of administered P^{32} retained per 100 c.c. of red blood cells, white blood cells and plasma of the normal individuals and of the patients are listed in table 2 and the red blood cell and

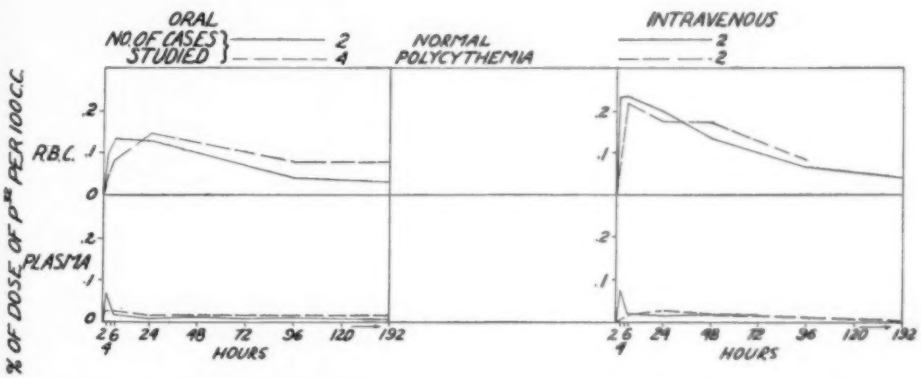

FIG. 1. Average retention of P^{32} administered orally and intravenously in red blood cells and plasma of normal individuals and patients with polycythemia.

plasma levels are illustrated in figure 1. The amounts and routes of administration of P^{32}, the number of cases studied and the intervals in time are noted also. No attempts were made to correct the findings for variations in the metabolic rate, blood volume, kidney and hepatic function, diet, age, weight, etc., of the cases studied. As can be observed in figure 1 the retention of radio-phosphorus in the red blood cells and plasma of both normal individuals and patients were nearly identical regardless of the route of administration. However, the retention of P^{32} in the red blood cells of both groups was higher following its administration by the intravenous route than by the oral route.

Table 3 presents the retention of P^{32} in various fractionations of red and white blood cells and plasma of two patients, one of whom (case 9) received the same number of millicuries of P^{32} on two occasions, once orally and once intravenously.

(*a*) Red blood cells. The levels of retention of P^{32} in the phospholipid fraction of the red blood cells of both patients increased during the 96-hour

TABLE I

	Name, Number, Sex and Age	Date of Admission, 1940 (Nos. 7 and 8, 1939)	Chief Complaints and Their Duration	Treatment before Admission	Physical Findings on Admission	Laboratory Findings on Admission: HB (%)	RBC (Thous.)	WBC (Thous.)	Platelets (Thous.)	Retics (%)	M = Marrow (Sternal Puncture) H = Hyperplastic Blood Volume	Treatment: Dates	Amount (Me) P^{32} Administered o. = Oral i.v. = Intravenously	Months after Initial Administration of Radio-phosphorus	Hematological Findings after Administration of P^{32}: HB (%)	RBC (Thous.)	WBC (Thous.)	Platelets (Thous.)	Retics (%)	Results as of April 1, 1941
	1, 2	3	4	5	6	7						8		9	10					11
Normal	1. Mie. M-43	5-27	Fracture—external malleolus	None	Normal male	77	4350	6				7-22-40	1.5 (o.)							No changes in blood levels during or following administration of P^{32} were noted in cases 1-4 inclusive.
Normal	2. Per. M-35	7-19	Fracture—external malleolus	None	Normal male	85	4900	8				7-22-40	1.5 (i.v.)							
Normal	3. Rob. M-31	3-25	Fracture—radius	None	Normal male	93	5100	7				7-22-40	1.5 (i.v.)							
Normal	4. Vic. M-32	6-17	Wire removed from fracture	None	Normal male	85	4840	6				7-22-40	1.5 (i.v.)							
	5. Hay. M-59	2-14	1. Headache 2. Plethora 3. Weakness 4. Mass and pain in upper left quad. 5. Loss of wt. } 2 yrs.	X-radiation at irregular intervals for 1 yr. preceding admission	1. Plethoric 2. Spleen fills entire left abdomen 3. Liver—2 cm. below costal margin 4. Hands very red	110	6600	55 Leukemoid reaction	340		M—H (differential findings within normal limits)	2-16-40 2-26-40 3-21-40 8-10-40 (o.)	5.96 8.16 7.00 8.00 29.12	3 6 9 12	86 100 106 115	5280 7890 6240	13 18 14 26	250		Symptomatic remission for 9 mo. Spleen 5 cm. below left costal margin—3 mo. R.B.C. level rising but no P^{32} administered since August, 1940.
	6. Knu. M-36	4-26	1. Headache 2. Weakness 3. Partial blindness 4. Hemiplegia (1939) } 3 yrs.	Numerous phlebotomies for a period of 1 yr. preceding admission	1. Plethoric 2. Retinal hemorrhages 3. Hands red 4. Spastic paralysis—left extremities 5. Bedridden	121	6900	40 Leukemoid reaction	600	1.4	M—H (shift to right in differential findings)	5-16-40 7-18-40 8-16-40 11-22-40 1- 3-41 (o.) 2-11-41 3- 4-41 (i.v.) 48.82	6.27 8.00 7.50 7.50 10.00 4.65 4.90	3 6 9 12	120 119 110 101	6920 6480 6590 5560	23 15 8 5	600 285 150 223	1.2 1.8 .6 .5	Symptomatic, clinical and hematological improvement—9 mo. Patient has been ambulatory for 9 mo.

Polycythemia	7. Lin. F-57	11–13	1. Dizziness 2. Headache 3. Plethora 4. Weakness 5. Staggering 6. Pain upper left quad. — 2 yrs.	Phlebotomies every 2 wks. for 1 yr. preceding admission	1. Plethoric 2. Spleen—tender (2 cm. below costal margin) 3. Hands red	129	7000	17	900	1.4	M—H (differential findings within normal limits)	11–24–39 12–12–39	5.34 7.00 (o.) 12.34	3 6 9 12 15	91 97 97 102 96	4680 4105 4600 4960 4870	8 9 13 12 10	280 330 239 168 301	.1 1.8 .8 .2 .2	Clinical, symptomatic and hematological remission of 1 yr's. duration. Spleen not palpable—1 yr.
	8. Par. F-42	11–17	1. Dizziness — 3 yrs. 2. Headache 3. Weakness 4. Plethora 5. Paresthesia of hands and feet — 2 yrs. 5. Backache	Phenylhydrazine and phlebotomies for period of 2 yrs.	1. Plethoric 2. Spleen—2 cm. below costal margin 3. Enlarged thyroid 4. Palms of hands very red	128	6630	16	1200	3.4	M—H (differential findings within normal limits)	11–17–39 12–13–39 1–22–41	5.2 7.9 5.0 (o.) 18.1	3 6 9 12 15	92 90 92 89 83	3910 4200 4650 4150 4360	6 6 7 6 9	226 90 130 481 400	1.5 1.5 .3 .6 1.4	Clinical, symptomatic and subjective improvement. Occasional headaches, but no dizziness or paresthesia—1 yr. Blood findings normal—1 yr. Spleen not palpable—1 yr.
	9. Wer. M–61	4–10	1. Headache — 3 yrs. 2. Weakness 3. Plethora 4. Blurred vision — 2 mo.	Numerous phlebotomies for 1 yr. preceding admission	1. Plethoric 2. Hands red 3. Retinal hemorrhages 4. Liver—1 cm. Spleen—6 cm. below costal margin	150	7800	17	400			4–14–40 7– 6–40 7– 7–40 7–25–40 10–15–40 12–17–40 1– 6–41 1–10–41 1–23–41 3–12–41 42.7	6.5 2.9 2.8 5.7 9.0 2.5 2.5 2.0 3.8 5.0 (i.v.)	3 6 9 12	147 119 134 109	6920 6525 6300 4980	6 8 14 7	440 727 310	1.4 .1 .3	Symptomatic and subjective remission—6 mo. Blood findings improved. Spleen 2 cm. below costal margin. Liver not palpable.
	10. Wil. F–65	8–12	1. Headache 2. Dizziness 3. Cyanosis 4. Weakness 5. Numbness of extremities — 8 yrs.	Phenylhydrazine and x-radiation in 1932. Phlebotomies since	1. Plethoric 2. Spleen—7 cm. below cost. marg. 3. Hands red 4. Retina—dusky hue, veins distended and tortuous	153	8330	12	188	0.2	M—H (Diff. findings within normal limits). Blood vol.—165 c.c./kilo.	8–21–40 9–16–40 10– 1–40 12–16–40 38.0	10.0 10.0 12.0 (o.) 6.0 (i.v.)	3 6 7	138 140 102	6700 6600 5020	12 6 5	150 142	2.0 1.0	Symptomatic and subjective improvement—6 mo. Blood findings improved—2 mo. Spleen not palpable—3 mo.

TABLE II

Rates of Absorption (Retention) of Radio-Phosphorus in Blood

	Periods after Oral Administration of P^{32}														Time (Days) for Values Under "Other"	Milligrams of Sodium Phosphate in Which P^{32} Was Incorporated	Microcuries of P^{32} Administered Orally	Name and No. of Case Receiving Radio-Phosphorus Orally
	2 Hours		4 Hours		6 Hours		24 Hours		48 Hours		96 Hours		Others					
	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%				
Normal Individuals																		
Whole blood	.0091	.0606			.0102	.0680	.0071	.0473	.0060	.0400	.0037	.0246	.0015	.0100				
R.B.C.	.0080	.0533			.0131	.0873	.0137	.0913	.0097	.0647	.0048	.0320	.0041	.0273				
W.B.C.	.0087	.0580			.0013	.0086	.0040	.0266	.0050	.0332	.0104	.0693	.0091	.0600	8	600	1500	Mie 1
Plasma	.0042	.0613			.0024	.0160	.0016	.0106	.0017	.0113	.0015	.0100	.0005	.0033				
Whole blood	.0192	.1280			.0206	.1373	.0150	.1000	.0128	.0853	.0089	.0593	.0045	.0300				
R.B.C.	.0215	.1433			.0263	.1753	.0249	.1660	.0170	.1133	.0080	.0533	.0049	.0326				
W.B.C.	.0104	.0693			.0090	.0600	.0131	.0873	.0369	.2460	.0319	.2126	.0340	.2270	8	600	1500	Rob 3
Plasma	.0123	.0820			.0039	.0260	.0032	.0215	.0032	.0215	.0032	.0215	.0019	.0126				

Polycythemic Patients

							Platelets										
Whole blood	—	—	—	—	—	—	.0630	.1056					—	—			
R.B.C.	.0173	.0290	.0320	.0540	.0480	.080	.0685	.1150					.0254	.042	10	2800	5960	Hay 5
W.B.C.	.0125	.0210	.0210	.0350	.0344	.0570	.0335	.0560					.080	.130				
Plasma	.0188	.0310	.0216	.0360	.0184	.0310	.0058	.0090					.0038	.006				
R.B.C. stroma							.000015	.00002			—	—	—	—				
R.B.C.							.091	.172			.051	.096	.042	.079	8	2330	5340	Lin 7
W.B.C.							—	—			—	—	—	—				
Plasma							.014	.026			.012	.022	.009	.017				
R.B.C. stroma							.000072	.00013			—	—	—	—				
R.B.C.							.094	.181			.048	.092	.035	.067	9	1800	5200	Par 8
W.B.C.							—	—			—	—	—	—				
Plasma							.013	.025			.010	.019	.009	.017				
Whole blood							.0256	.100	.0195	.0764	.0142	.0556	.0087	.0341				
R.B.C. stroma							imm.*		imm.*		imm.*		—					
R.B.C.							.0312	.122	.0231	.0905	.0167	.0655	.0065	.0255	21	178	2550	Wer 9
Plasma							.0052	.0204	.0051	.020	.0048	.0188	.002	.00785				

* immeasurable.

TABLE II (*Continued*)

	Name and Number of Patient Receiving P^{32} Both Orally and Intravenously	Interval in Days Between Oral and Intravenous Administrations	Name and Number of Patient Receiving P^{32} Intravenously	Microcuries of P^{32} Administered Intravenously	Milligrams of Sodium Phosphate in Which P^{32} Was Incorporated	Periods after Intravenous Administration of P^{32}												Time (Days) for Values Under "Other"
						2 Hours		6 Hours		24 Hours		48 Hours		96 Hours		Others		
						Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	
Normal Individuals																		
Whole blood			Per 2	1500	600	.0251	.1673	.0249	.1660	.0350	.2330	.0120	.0800	.0058	.0386	.0037	.0240	8
R.B.C.						.0336	.2240	.0349	.2326	.0315	.2100	.0198	.1320	.0091	.0606	.0047	.0313	
W.B.C.						.0401	.2673	.0114	.0760	.0171	.1140	.0160	.1070	.0170	.1133	.0340	.2270	
Plasma						.0096	.0640	.0038	.0253	.0023	.0153	.0030	.0207	.0019	.0126	.0009	.0060	
Whole blood			Vic 4	1500	600	.0260	.1733	.0257	.1713	.0168	.1120			.0033	.0220	.0042	.0280	8
R.B.C.						.0340	.2266	.0352	.2346	.0283	.1886			.0117	.0780	.0071	.0470	
W.B.C.						.0274	.1822	.0110	.0733	.0113	.0753			.0168	.1120	.0200	.1330	
Plasma						.0131	.0873	.0028	.0186	.0036	.0240			.0026	.0173	.0013	.0080	

Polycythemic Patients

Whole blood	Wer 9	21		2550	167					.0306	.120	.0212	.083	.0195	.0764			
R.B.C. stroma										—		—		—				
R.B.C.										.036	.141	.0518	.203	.0173	.0679			
Plasma										.005	.0196	.003	.0118	.005	.0196			
Whole blood			Wilk 10	6000	420			.0495	.0825	.0453	.0755	.0370	.0617	.0361	.0602			
R.B.C. stroma										—		.00164	.0027	.00047	.00078			
R.B.C.								.1260	.210	.130	.217	.0875	.146	.0602	.100			
Plasma								.0146	.0243	.0204	.0340	.0130	.0217	.0083	.0138			

Activities corrected for decay and to date of administration.
Total amounts expressed in microcuries per c.c.; percentages in % of dose per 100 c.c.

TABLE III

Retention of P^{32} in the Phospholipid, Acid Soluble and Nucleoprotein Fractions of R.B.C., W.B.C. and Plasma of Two Patients with Polycythemia (Expressed in μc per c.c. of R.B.C., W.B.C. or Plasma)

Case No.	Hrs. after Adm.	Amt. (in Microcuries) of P^{32} Adm.	Amt. (in gm.) of Sod. Phos. in Which P^{32} Was Incorp.	Route of Adm.	R.B.C.			W.B.C.			Plasma		
					Phospho	Acid S	Nucleo	Phospho	Acid S	Nucleo	Phospho	Acid S	Nucleo
9	24	2550	0.1785	Oral	0.0004	0.0212	0.0135	0.0042	0.0150	0.0026	0.0011	0.0018	0.0009
	48				0.0007	0.0188	0.0070	0.0022	0.0193	0.0140	0.0018	0.0032	0.0014
	96				0.0008	0.0172	0.0055	0.0099	0.0182	0.0145	0.0024	0.0018	0.0002
	—												
	21 Da				0.0012	0.0026	0.0007	0.0041	0.0045	0.0045	0.0015	0.0004	0.0002
9	24	2550	0.167	I.V.	0.0024	0.0399	0.0009	0.0115	0.0181	0.0028	0.0028	0.0022	0.0004
	48				0.0028	0.0276	0.0072	0.0221	0.0571	0.0092	0.0092	0.0018	0.0004
	96				0.0025	0.0051	0.0051	0.0370	0.0239	0.0043	0.0043	0.0016	0.0005
10	12	6000	0.420	I.V.	0.0010	0.124	0.0137	0.0103	0.1005	0.0155	0.0019	0.0113	0.0012
	24				0.0012	0.0930	0.0727	0.0224	0.1090	0.0233	0.0045	0.0076	0.0029
	48				0.0022	0.0900	0.0462	0.0219	0.1210	0.0511	0.0079	0.0055	0.0022
	96				0.0047	0.0486	0.0323	0.0091	0.0654	0.0450	0.0101	0.0047	0.0042

TABLE IV

The Retention of Radio-Phosphorus in the Stroma of Red Blood Cells

Case No.	Amount (in microcuries) and route of P^{32} administered O = orally I.V. = intravenously	Days between adm. and withdrawal of blood for fractionations	Amount of P^{32} in microcuries per 100 c.c. of packed R.B.C. (Centrifuged 20 min. at 1450 ×gravity)	
			Hemoglobin Fraction	Stroma
9	2500 (O)	1	.977	immeasurable
		2	.740	"
10	6000 (I.V.)	2	10.2	.164
		4	7.45	.0474
8	7900 (O)	21	.492	.0072
7	7000 (O)	22	.672	.0015

period (and probably during the 4 to 21-day period) while those of the acid soluble and nucleoprotein fractions decreased after the 24–48 hour period.

(*b*) White blood cells. The level of retention of P^{32} in the phospholipid fraction of the white blood cells of case 9 increased and that of case 10 decreased during the 96-hour period. Those of the acid soluble and nucleoprotein fractions appeared to reach a peak between the forty-eighth and ninety-sixth hour in both patients regardless of route of administration.

(*c*) Plasma. The level of retention of P^{32} in the phospholipid fraction of the plasma of the patients apparently reached a peak between the forty-eighth and ninety-sixth hours, while that of the acid soluble reached a peak

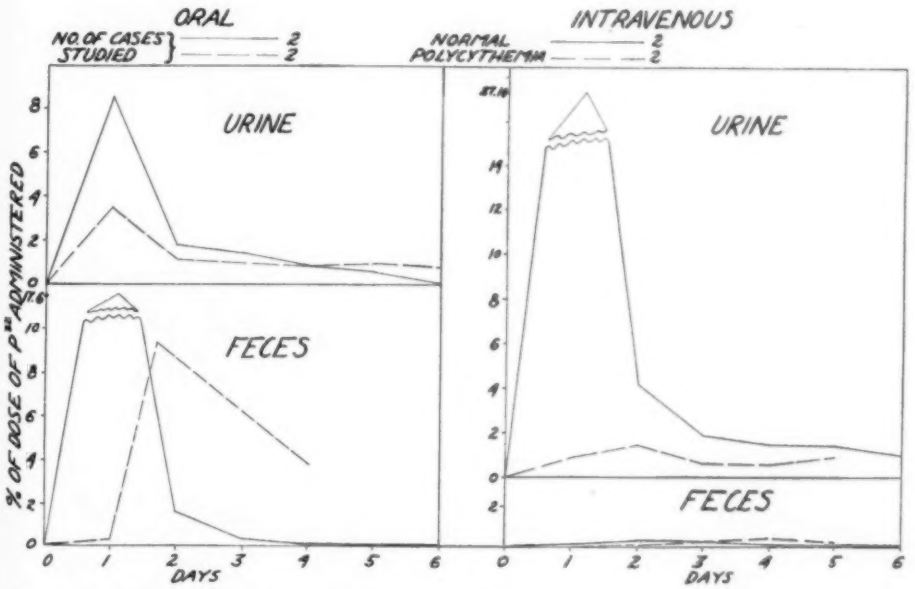

FIG. 2. Average excretion of P^{32} in urine and feces of normal individuals and patients with polycythemia.

TABLE V

Rates of Excretion of Radio-Phosphorus in Urine and Feces

	Periods after Oral Administration of P^{32}														Milligrams of Sodium Phosphate in Which P^{32} Was Incorporated	Microcuries of P^{32} Administered Orally	Name and Number of Patients Receiving Radio-Phosphorus Orally
	1 Day		2 Days		3 Days		4 Days		5 Days		6 Days		Total Excretion				
	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total 4–6 Days	%			
Normal Individuals																	
Urine	69.5	4.63	25.5	1.7	13.4	.89	10.9	.72	11.1	.74	6.75	.45	344	22.9	600	1500	Mie. 1
Stool	194.0	12.93	7.8	.52	3.32	.22	.41	.02			.95	.06					
Urine	191.19	12.7	29.5	1.96	31.8	2.12	17.34	1.15	21.22	1.41	16.9	1.12	695	46.3	600	1500	Rob. 3
Stool	338.98	22.59	38.8	2.59	5.85	.39	3.05	.10	.14	.01	.18	.01					
Polycythemic Patients																	
Urine	35.76	.6	17.88	.3	11.92	.2	11.92	.2	25.96	.1	25.96	.1	1488	25.1	2800	5960	Hay. 5
Stool			911.9	15.3			447.0	7.5									
Urine	173.0	6.79	56.9	2.23	23.3	.91	43.4	1.70					400.96	15.7	178	2550	Wer. 9
Stool	6.01	.24	80.5	3.16	14.0	.55	3.85	.15									

TABLE V—*Continued*

	Name and Number of Patient Receiving P^{32} Orally and Intravenously	Interval in Days Between Oral and Intravenous Administrations	Name and Number of Patients Receiving Radio-Phosphorus Intravenously	Microcuries of P^{32} Administered Intravenously	Milligrams of Sodium Phosphate in Which P^{32} Was Incorporated	Periods after Intravenous Administration of P^{32}													
						1 Day		2 Days		3 Days		4 Days		5 Days		6 Days		Total Excretion	
						Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total 4–6 Days	%
Normal Individuals																			
Urine			Per. 2	1500	600	565.2	37.66	75.5	5.03	37.3	2.48	25.41	1.69	26.16	1.74	17.49	1.16	760	50.5
Stool						1.47	.098	3.87	.25	3.72	.24	2.49	.16	.35	.02	.77	.05		
Urine			Vic. 4	1500	600	250.0	16.66	52.5	3.5	22.6	1.5	22.2	1.48	19.11	1.27	16.0	1.06	391	26.1
Stool						1.29	.08	6.74	.45					.30	.02	.15	.01		
Polycythemic Patients																			
Urine	Wer. 9	21		2550	167	25.6	1.00	58.8	2.31	36.8	1.44	23.2	.91					164.97	6.46
Stool						1.12	.04	5.32	.21	7.23	.28	6.9	.27						
Urine			Wilk. 10	6000	420	Lost		63.7	1.06	13.9	.23	47.0	.78	74.1	1.23			251.4 +	4.18 +
Stool						Lost		3.35	.06	—		31.6	.53	17.8	.30				

Activities corrected for decay and to date of administration. Total amounts and percentages of doses expressed in microcuries.

before the forty-eighth hour, and that of the nucleoprotein fraction varied considerably.

In case 9, to whom equal amounts of P^{32} were administered both orally and intravenously, the great majority of the fractionations of the blood retained proportionately more radio-phosphorus after its administration by the latter route.

Table 4 indicates that very small quantities of radio-phosphorus are found in the stroma of red blood cells. In the few findings presented, there is apparently no distinct correlation between the concentrations of radio-phosphorus in the stroma and hemoglobin fractions in relation to the time element.

Table 5 and figure 2 indicate the average per cent of the dose of administered P^{32} excreted in the urine and feces of normal individuals and patients with polycythemia. The normal individuals excreted from 25 to 50 per cent of the dose of P^{32} during the 6 days following its administration regardless of the route. However, during a period of 4 to 6 days the patients excreted less than 25 per cent of the dose. The patients excreted less P^{32} in both the urine and feces, regardless of the route of administration, than did the normal individuals.

Discussion

Radio-phosphorus, which emits beta-particles which can be accurately quantitated, can be used as a "tracer" or a therapeutic agent.* The beta particles have the capacity of producing ionization, just as do roentgen-rays, and therefore the effects of radio-phosphorus are fundamentally and basically similar to those of x-radiation. However, radio-phosphorus concentrates in bone marrow [6, 7, 8] and since it has a half-life of 14.3 days it can constantly bombard with radiation a tissue, in which it concentrates, for many days. It is this latter feature that is probably responsible for the favorable hematological results obtained in the patients with polycythemia. In three of the patients (cases 6, 9 and 10) fairly large doses of radio-phosphorus had to be administered intravenously before a decrease in the hemoglobin levels took place. Presumably the concentration of P^{32} did not reach sufficiently high levels following oral administrations to reduce the production or release of red blood cells. The first evidence of significant decreases in the hemoglobin levels occurred approximately 100 days † after an effective dose (this depended upon the quantity and/or route of administration) of radio-phosphorus had been administered. Since radio-phosphorus has never produced

* The so-called "safe tracer dose" which has been studied in animals [9] has not yet been studied in humans. Presumably, in the normal cases studied here, "radiation effects" have occurred and therefore accurate qualitative or quantitative deductions regarding phosphorus metabolism cannot be made.

It is known, from experiments upon both animals and human beings, that relatively large doses of sodium phosphate when accompanied with radio-phosphorus, reduce the amount of P^{32} retained by the blood. Therefore this variable would also alter deductions.

† The usual life span of an average human red blood cell.

nausea, vomiting or any clinical ill effects after its administration this form of therapy seems acceptable at the present time. Perhaps other radioactive agents will be found to be superior. It should be reëmphasized that the physical and clinical improvement of the patients was as remarkable as the hematological improvement.

If corrections for variations in blood volume, weight, etc. of the patients were made, the absorption levels would be different but the trends would be the same. Greater concentrations of P^{32} are found in the blood (and therefore the marrow) when radio-phosphorus is administered intravenously than when given orally.

The findings, presented above, of the fractionation of red blood cells are too incomplete to make deductions. However, it is interesting to note that the amounts of P^{32} found in the phospholipid fractions of the red blood cells of case 9 were much less than those of case 10. Since it is well known that the stroma of red blood cells is composed of substances lipoidal in character, it can be observed (tables 2 and 4) that the fraction containing the stroma of the red cells of case 9 retained immeasurably small amounts of P^{32} while that of case 10 retained approximately 1 per cent of all of the P^{32} of the red blood cells. This difference may be due to the increased quantity of P^{32} administered, to routes of administration, or even to differences in red cell or hemoglobin structure or production. It appears therefore that phosphorus ultimately reaches the stroma presumably after passing through the hemoglobin fraction. In general, however, less than 1 per cent of the P^{32} retained by red blood cells is found in the stroma.

The explanation is unknown for the lesser excretion of P^{32} from the patients with polycythemia than that from normal individuals. It can only be assumed that the tissues of the patients had greater need or affinity for the phosphorus or that the P^{32} was retained by the tissues for longer periods of time.

Conclusions

1. The distribution of P^{32} in various fractions of blood and the rates of excretion of P^{32} in the urine and feces of normal individuals and patients with polycythemia are presented.

2. Evidence is presented that marked clinical and hematological improvement in patients with polycythemia follows the administration of "therapeutic" doses of radio-phosphorus.

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EXPERIENCES IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH SULFANILAMIDE, SULFAPYRIDINE AND SULFATHIAZOLE; A REVIEW OF PREVIOUSLY REPORTED CURED CASES WITH THE REPORT OF FIFTEEN TREATED CASES INCLUDING ONE CURE AND ONE ABORTED CASE *

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The advent of new chemo-therapeutic agents has provided the physician weapons with which to combat infectious endocarditis. While the majority of cases treated with sulfanilamide and its derivatives progress to a fatal issue, a definite minority have been shown to reach a stage of apparent clinical cure. Thirty-one cases which have been cured by the use of sulfanilamide and its derivatives have been gathered from the literature. For convenience the essential data have been collected in tabular form (chart 1). Undoubtedly, other additions will be made as chemotherapy becomes a more generally utilized means of treatment. In addition to the 26 cured cases listed below, Long and Bliss [1] have reported five cases cured by sulfanilamide. Four of the five occurred in patients with congenital heart lesions. Because detailed clinical histories are not available, they have not been added to this collection.

The diagnosis of bacterial endocarditis is based on a well recognized clinical picture which needs no discussion. If one is to have confidence in it then certain postulations should be made. One should find in the patient a valvulitis or a congenital cardiac anomaly. If to this is added a positive blood culture, the case may be regarded as proved. If the blood culture is negative, splenomegaly with or without embolic manifestations is required to complete the diagnosis. In the cases of Major and Leger, and Kelson and White there was pathological proof of the cure, since the patients afterwards died of congestive heart failure and were examined post mortem. It is of interest to note that three of the 19 cases had congenital lesions, and 16 rheumatic valvulitis. In 12 cases *Streptococcus viridans* was recovered and in two a hemolytic streptococcus. In three patients the blood culture was sterile. The longest periods of observation at the time of the report were 15 and 18 months. Even though the periods of observation in the other cases were much shorter, the changes produced in the clinical pictures by the

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treatment were sufficient to justify the assumption that a clinical cure had been accomplished. The accumulating evidence, therefore, suggests that in a few cases cures are being obtained and that ways and means may yet be found for making the sulfonamide derivatives more effective. For this reason the experience obtained in treating 15 cases over the last two and one-half years will be summarized. In addition to these, two cases will be reported in detail; in one a clinical cure was obtained and in the other a beginning valvular implantation seemed to have been aborted.

Results of Treatment

Fifteen cases have been treated by sulfanilamide, sulfapyridine or sulfathiazole, in the medical ward in the Research and Educational Hospital during the last three years. The series comprises seven women and eight

CHART I

Subacute Bacterial Endocarditis; Recovery from Therapy with Sulfanilamide and Its Derivatives

Author	Patient Age-Sex	Blood Culture	Cardiac Diagnosis	Splenomegaly	Embolic Phenomena	Therapy	Period of Observation at Time of Publication
1. Klee, Römer [2] 1935	* *	Sterile	Endocarditis	Present	*	Prontosil	8 weeks
2. McQuarrie [3] 1937	6 M	Streptococcus (type?)	R.H.D.* with mitral sten. and insuff.	*	*	Prontylin	66 days
3. Hussey [4] 1937	34 M	Hemolytic strept.	R.H.D. with mitral and aortic stenosis	Present	Absent	Sulfanil.	11 weeks
4. Major and Leger [5] 1938	39 F	*Strept. viridans*	R.H.D. with mitral and aortic insuff.	Present	Present	Prontosil and sulfanil.	Death from cardiac failure after 29 days of normal temperature.
5. Manson-Bahr [6] 1938	60 M	Sterile	Endocarditis (R.H.D. with mitral sten.? and possible aortic sten.?)	Absent	Absent	Prontosil	2 years
6. Manson-Bahr [6] 1938	45 M	Sterile	Endocarditis	Present	Absent	Prontosil	15 months
7. Major and Leger [7] 1939	36 M	*Strept. viridans*	R.H.D. with mitral sten. and insuff.	Present	*	Neo-prontosil, and sulfapyridine, and prontosil	1 year
8. Spink and Crago [8] 1939	18 F	*Strept. viridans*	Patent ductus arter.	Present	Present	Sulfanil.	9 months
9. Barton and Stinger [9] 1939	4 F	*Strept. viridans*	Prob. congenital heart	Present	Present	Sulfanil.	3 months
10. Kelson and White [10] 1939	22 M	Positive	*	*	*	Sulfapyridine and heparin	6 months
11. Kelson and White [10]	23 F	Positive	R.H.D. with mitral lesion	*	*	Sulfapyridine plus heparin	6 months Death from cardiac failure
12. Kelson and White [10] 1939	41 M	Positive	*	*	*	Sulfapyridine plus heparin	4 months
13. Andrews [11] 1940	68 M	Sterile	Aortic insuff. (etiol.?)	Present	Present	Sulfapyridine	

CHART I—*Continued*

Author	Patient Age-Sex	Blood Culture	Cardiac Diagnosis	Splenomegaly	Embolic Phenomena	Therapy	Period of Observation at Time of Publication
14. Lippmann [12] 1940	53 M	*Streptococcus viridans*	R.H.D.(?)	Present	Present	Sulfanil., neoprontosil and sulfapyridine with ammonium heptenchlorarsonate (arsenical)	3½ months
15. Heyman [13] 1940	38 F	*Streptococcus viridans*	Patent ductus arter.	*	Present	Sulfanilamide orally	18 months
16. Major [14] 1940	40 F	*Strept. viridans*	R.H.D.(?)	Present	Absent	Sulfapyridine	7 months
17. Christie [15] 1940	17 F	*Strept. viridans*	R.H.D. with mitral insuff.	Present	Present	Sulfanil.	1 year
18. Alexander S., [16] Alexander, S. F. 1940	62 M	Hemoly. strept.	Mitral valvulitis	Absent	Absent	Sulfanil. orally	4 months
19. Orgain and Poston [17] 1940	21 F	*Strept. vir.* and *N. gonorrh.*	*	Absent	Present	Sulfanil. and Sulfapyridine	7 months
20. Bierman and Baehr [46]	32 M	*Strept. vir.*	Endocarditis	Absent	Present	Sulfanil. and fever therapy	Over 2 years
21. Bierman and Baehr [46]	19 F	*B. influenzae*	Endocarditis	Present	Present	Sulfanil. and fever therapy	10 months
22. Solomon [47]	19 F	*Strept. vir.*	R.H.D. with mitral sten. and insuff.	Present	Present	Sulfanil. and typhoparatyphoid vaccine	18 months
23. Solomon [47]	40 M	Nonhemolytic strept.	R.H.D. with mitral and aortic sten. and insuff.	Present	Present	Sulfanil. and typhoparatyphoid vaccine	2 months
24. Solomon [47]	19 F	*Strept. vir.*	R.H.D. with mitral insuff. and aortic sten. and insuff.	Present	Present	Sulfapyridine and typhoparatyphoid vaccine	5 months
25. Solomon [47]	14 M	*Strept. vir.*	R.H.D. with mitral and aortic insuff.	Present	Present	Sulfapyridine and typhoparatyphoid vaccine	2 months
26. Solomon [47]	37 M	Sterile	R.H.D. with aortic sten. and insuff.	Present	Present	Sulfapyridine and typhoparatyphoid vaccine	2 months

(R.H.D. = Rheumatic heart disease.)

men the ages varying between 21 and 60 years. Thirteen patients were diagnosed clinically as rheumatic heart disease, one as a coarctation of the aorta, and one as hypertensive heart disease. Frequent hemoglobin determinations, and red and white cell counts were made. Blood levels of sulfanilamide, sulfapyridine and sulfathiazole were also determined in order to obtain maximum therapeutic concentrations. Blood cultures drawn were incubated for a period of three weeks before being pronounced sterile.

Chart 2 presents the essential data concerning treatment and its effects in tabular form.

CASE REPORTS

Case 8. A white female of Roumanian descent, aged 19, who had previously been well aside from slight dyspnea on stair climbing, was admitted on June 18, 1938, to the Research and Educational Hospital complaining of severe right lumbar

CHART II

No.	Age-Sex	Cardiac Diagnosis	Splenomegaly	Blood Cultures	Embolic Manifestations	Total Medication	Duration Treatment	Results Treatment	Pathological Findings
1.	28 F	R.H.D. with mitral sten. and regurg.	Present	*Strept. viridans*	Present	Sulfanilamide 37 gm.	11 days	Death 9 mos.	No postmortem
2.	35 M	R.H.D. with mitral sten. and regurg.	Present	*Strept. viridans*	Present	Sulfanilamide 64.6 gm.	18 days	Death 5½ mos.	Mitral stenosis. Vegetations on mitral valve. "Septic spleen." Multiple infarcts
3.	33 F	R.H.D. with mitral insuff. Mild diabetes	Present	Sterile	Present	Sulfanilamide 6.6 gm.	4 days	Death 14 mos.	No postmortem
4.	23 M	R.H.D. with mitral sten. and insuff. and aortic insuff.	Present	*Strept. viridans*	Present	Sulfapyridine 72 gm. Sulfanilamide 6.6 gm.	18 days 3 days	Death 3½ mos.	No postmortem
5.	31 M	R.H.D. with mitral sten. and insuff.	Present	*Strept. viridans*	Present	Sulfanilamide 38 gm.	13 days	Death	No postmortem
6.	31 F	R.H.D. with mitral sten. and insuff.	Absent	*Strept. viridans*	Present	Sulfanilamide 88.8 gm.	24 days	Death 22 mos.	Mitral stenosis. Vegetations on mitral valve with ulcerations. Multiple infarcts
7.	36 M	R.H.D. with mitral sten. and insuff.	Present	*Strept. viridans*	Present	Sulfanilamide 26 gm. Sulfapyridine 150 gm.	9 days 47 days	Death 6½ mos.	Mitral and tricuspid stenosis. Vegetations on mitral valve. Multiple infarcts. Cerebral hemorrhage
8.	21 F	Coarctation of aorta	Present	*Strept. viridans*	Present	Sulfanilamide 58 gm.	17 days	Clinical cure 2 yrs. 9 mos.	
9.	27 F	R.H.D. with mitral sten. and insuff.	Present	*Strept. viridans*	Present	Sulfapyridine 81 gm.	31 days	Death 6 mos.	Mitral stenosis. Vegetations on mitral, aortic and tricuspid valves. Multiple infarcts
10.	21 M	R.H.D. with mitral sten. and insuff. and aortic insuff.	Present	Sterile	Present	Sulfapyridine 97 gm. Sulfathiazole 18 gm.	31 days 6 days	Death	Mitral stenosis. Vegetations on mitral valve. Multiple infarcts
11.	60 M	Hypertensive ht. disease	Present	*Diplococcus pneumoniae*	Present	Sulfanilamide 16 gm.	4 days	Death 1 mo.	Vegetations on tricuspid and aortic valves. Arteriosclerosis of aorta and coronary arteries
12.	50 F	R.H.D. with mitral sten. and insuff.	Present	Sterile	Present	Sulfapyridine 9 gm.	5 days	Death 18 mos.	Mitral and aortic stenosis. Vegetations of mitral valve. Multiple infarcts
13.	35 F	R.H.D. with mitral sten.	Present	Sterile	Present	Sulfanilamide 30 gm. Sulfathiazole 17 gm.	5 days 3 days	Well during 5th mo.	
14.	32 M	R.H.D. with mitral sten. and insuff.	Present	*Strept. viridans*	Present	Sulfathiazole 82 gm.	18 days	Alive during 4th month. Some fever	
15.	41 M	R.H.D. with aortic sten. and regurg., mitral sten. and regurg.	Present	*Strept. viridans*	Present	Sulfathiazole 500 gm. Sulfapyridine 120 gm.	4½ mos. 30 days	Alive during 8th month. Some fever	

pain of six weeks' duration. This was accompanied by fatigue, weakness and weight loss. Six weeks before entrance the patient had a sudden sharp pain in the right lumbar region, accompanied by vomiting so severe as to cause her to "double up." She had spent three weeks at the Cook County Hospital (service of Dr. H. J. Isaacs) where a diagnosis of subacute bacterial endocarditis with a coarctation of the aorta was made. Two positive blood cultures, one of *Streptococcus viridans*, and one

of *Streptococcus hemolyticus*, were obtained there. The patient was discharged from the County Hospital with pain in the right kidney region unchanged, and fever.

The day preceding admittance to Research and Educational Hospital she had a severe chill lasting 10 minutes. The lumbar pain was very severe, accentuated during urination, and the urine was tinged with blood.

The past history included scarlet fever and pneumonia in childhood, measles, mumps, whooping cough and chickenpox, but no rheumatic fever or sore throats. The patient was poorly nourished, appeared acutely ill and in severe pain, holding the right side. On admittance she had a temperature of 101.6°, blood pressure 190 mm. Hg systolic and 110 mm. diastolic in both arms, pulse 134, respiration 26. The lungs were clear. The heart was enlarged slightly to the left, with a harsh systolic murmur at the apex, and a distinct, softer systolic murmur at the base, heard best at the third left interspace. Marked tenderness over the right lumbar area was noticed, but no muscle spasm.

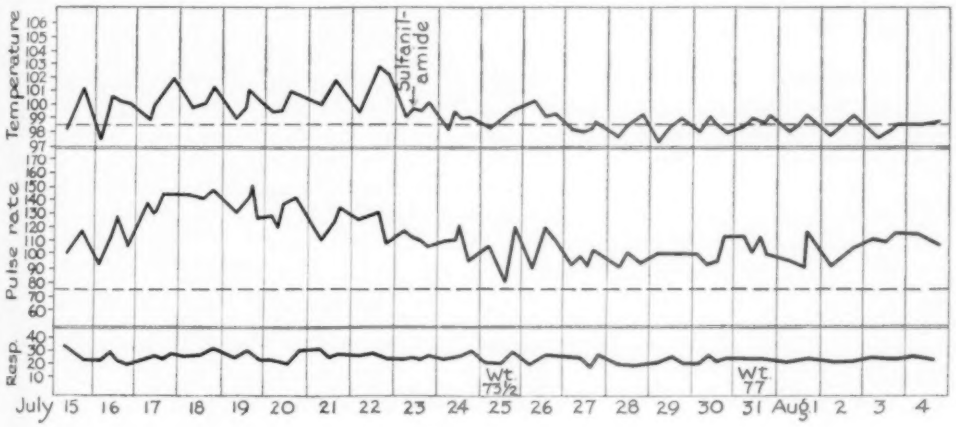

FIG. 1.

Femoral and dorsal pedal artery pulsations were not perceptible, and the blood pressure in the thighs could not be obtained.

The blood study revealed 11.5 gm. of hemoglobin, 3,740,000 red cells and 19,500 white cells per cu. mm. A catheterized specimen of urine contained innumerable red cells and many leukocytes. The blood also showed non-protein nitrogen 24 mg. and urea nitrogen 12 mg. Roentgenograms of the chest revealed notching of the ribs, with a normal cardiac size and configuration.

Although the right lumbar pain diminished in the next 24 hours, the patient ran a septic temperature to 101–104° for five weeks. Splenic tumor was palpated on July 8. Blood cultures on July 7 and 15 revealed a *Streptococcus viridans*. On July 17 she complained of a severe pain in the left upper quadrant with local tenderness which was attributed to an infarct of the spleen. Rapid wasting brought her weight to 73 lbs. on July 23.

On July 23 the patient was placed on 4 gm. of sulfanilamide daily. The day sulfanilamide was begun, a marked drop in the fever occurred (see figure 1) and during the following 16 days this dose was continued. The fever disappeared, the patient improved markedly in strength and vigor, and gained 3½ lbs. in weight. During sulfanilamide therapy the hemoglobin dropped from 10.7 gm. to 7 gm., and the patient was given 400 c.c. of blood on July 30, 1939.

Two weeks after the initial dose of sulfanilamide, she was ambulatory and the spleen was no longer palpable. A total of 65.3 gm. of the drug was given between July 23 and August 8.

Blood cultures obtained on August 9, 15, 17, 24 and September 12, revealed no growth of organisms.

The patient remained in the hospital until November 11, 1939 gaining in weight up to 93½ lbs., feeling well and exhibiting only occasional temperatures up to 99.2 to 99.6°. During the two years and nine months following the beginning of treatment the patient has remained well. She has been readmitted five times merely for purposes of observation. On one occasion, four months after treatment was stopped, a small hemolytic atypical streptococcus was isolated from the blood. Thirty-four blood cultures taken during the two years following, failed to show any growth of organisms. Splenomegaly and embolic manifestations have been absent, and the patient feels well in every respect.

When last heard from, the patient was leading the life of her people (being a gypsy) and was well enough to travel from Chicago to California by auto-trailer, without any ill effects.

This patient is of interest because of the long period of observation—two years and nine months—longer than any case treated with sulfanilamide previously reported in the literature that has come to our attention.

Case 13. M. B., a 35 year old nurse, single, was first admitted to the hospital on October 20, 1940 for treatment of an acute erysipelas of the right ear, cheek and neck, of 24 hours' duration. The tissues were edematous, raised, reddened, and large glands were palpable at the angle of the right jaw. The temperature rectally was 103.8° and the pulse 124 per minute. A mitral configuration of the heart with a presystolic thrill and murmur was found. No murmurs were audible at the base of the heart. The spleen was not palpable. The urine was clear; the white cell count 14,400 per cu. mm.

The past history revealed three attacks of rheumatic fever during childhood and one of chorea. Pneumonia had occurred at 21 years, and a chronic sinus infection at age 28 years. An acute attack of pyelitis had occurred 4 years previously. For about 5 years she had suffered from chronic eczema of both external auditory canals.

Within 4 hours the fever had reached 106° rectally. The patient was given sulfanilamide by mouth, and was given a roentgen-ray treatment to the area of skin involved. She was also given 100 c.c. of convalescent scarlet fever serum intravenously. Her temperature then began to drop and by the third day was normal. Sulfanilamide levels of 7.1 mg. and 4.7 mg. were found on the morning of the second and third hospital days. Because of nausea, the sulfanilamide was stopped on the third day, after 13.3 gm. had been administered. A blood culture drawn on the first hospital day was sterile. She was given a second and third roentgen-ray treatment to the affected region. She was discharged on the ninth hospital day with a diagnosis of erysipelas. At this time the local lesion was completely resolved.

On November 5, eight days after the previous discharge, she was readmitted with a similar lesion of the left ear, cheek and neck. The edema and redness were very marked, but the line of demarcation between diseased and blotchy skin was less pronounced than before. Large glands also appeared at the angle of the left jaw. The lungs were clear, the heart murmurs unchanged, the spleen was not felt. The temperature was 104° rectally on admission. Sulfanilamide was begun by mouth, and the patient was given 6.6 gm. plus 4,000 c.c. of intravenous fluids and a roentgen-ray treatment during the first 12 hours. By the following day the temperature was 101.4° but the patient was very nauseated. She managed to retain 5.5 gm. of sulfanilamide and was given 4,000 c.c. of intravenous fluids, and a roentgen-ray treatment. At

4:30 p.m. on the second hospital day, she developed a severe chill with an elevation in temperature to 104.5° rectally. At this time the heart seemed to be slightly enlarged and intravenous fluids were discontinued. One hundred c.c. of human scarlet fever convalescent serum were given intravenously. On the third hospital day the patient experienced a second and a third severe chill with the fever reaching 105.4° rectally. Intravenous administration of sulfanilamide was begun and 4 gm. of the drug were given by vein. A second dose of 100 c.c. of convalescent scarlet fever serum was given and a third roentgen-ray treatment. The lesion over the left ear and cheek was much less reddened and swollen, and was definitely regressing. In spite of the improvement in the local skin lesion, the fever continued high and the chills persisted.

On the fourth hospital day evidences of pulmonary congestion appeared. Because of nausea, digalen was given subcutaneously and caffeine sodium benzoate intravenously. Slight cyanosis and icterus were noted. The patient was semicomatose and irresponsive. On this day 12 gm. of sulfanilamide were given intravenously and the patient was given a 550 c.c. transfusion of blood. In spite of an adequate amount of fluid by vein, the temperature reached 106° rectally by evening. At this time the erysipelas had completely subsided.

On the fifth day the spleen was palpable for the first time. After 2 gm. of sulfanilamide had been given intravenously without improvement, it was discontinued and sodium sulfathiazole begun in doses of 3 gm. per 1000 c.c. of 10 per cent glucose, given as a slow drip by vein. From this time on, the temperature began to fall (see figure 3), and reached normal by afternoon of the sixth day. The improvement in her general condition was dramatic. During the sixth to the tenth hospital days the spleen was definitely palpable, two fingers below the costal arch, but by the twelfth day, was no longer felt.

On the fifteenth hospital day a faint reflux aortic diastolic murmur appeared for the first time. From the tenth to the twenty-first day the patient had temperatures reaching to 99.8° rectally, but the spleen was no longer palpable and at present, during the fifth month, she feels well. Five blood cultures taken since treatment have so far failed to show any growth.

During treatment sulfanilamide levels from 4.6 to 10.7 mg. (total sulfanilamide) were obtained. Sulfathiazole levels varied between 1 mg. and 3.85 mg. A total of 30 gm. of sulfanilamide and 17 gm. of sulfathiazole were given during the second admission.

Following the regression of the skin lesion the patient had remained desperately ill. The spleen had continued to enlarge and the sepsis was profound. It may be presumed that an implantation on the heart valve had occurred and that the persistent fever and splenomegaly were due to vegetations containing the hemolytic streptococcus. The development of the reflux aortic diastolic murmur during the period of her illness (it having been absent previously) is further evidence of acute valvular changes. The promptness with which chemotherapy was instituted after the illness began probably prevented extensive vegetative growths. The response to sulfathiazole, after sulfanilamide had failed to cause a remission, is of especial interest.

Effect of Treatment on Fatal Cases

Effect on Temperature. Among the 13 remaining cases, the most marked and striking effect was the fall in temperature which followed the administration of these drugs. This drop in temperature was most marked

with sulfapyridine, but also occurred, although to a less marked degree, with sulfanilamide and sulfathiazole. Five cases were treated with sulfapyridine and three showed a prompt and rather marked decrease in temperature. The single case in which sulfapyridine did not result in a fall in temperature was moribund when therapy was begun. Of seven cases treated with sulfanilamide alone, six revealed a fall in temperature and one revealed a slight elevation in fever.

Of the five cases treated with sulfapyridine, two also were given a separate trial course of sulfanilamide, and two cases a course of sulfathiazole. Case 7 (chart 2) revealed a rise in temperature with the administration of sulfanilamide, followed by a fall below the previous level of fever when sulfapyridine was begun. Case 4 revealed a fall in fever with both sulfanilamide and sulfapyridine. Case 10, which had been originally treated with sulfapyridine with a decrease in fever, was treated with sulfathiazole beginning six days before death. The patient's temperature fell to normal levels within 48 hours, but he expired from inanition and circulatory failure on the sixth day of treatment. Case 13 revealed no change in the level of temperature with sulfanilamide, but had a prompt fall to normal levels with sulfathiazole.

Effect on Clinical Course of Fatal Cases. The total duration of the fatal cases varied from one month to two years. The average duration of these cases was 8.9 months. This falls within the possible life expectancy of this disease and, as a group, no significant prolongation of life was found.

Case 7 gave the best clinical response among the fatal group, a complete remission of three weeks being produced. During this time the temperature was slightly elevated on only three occasions, and he gained in strength and was subjectively symptom-free. The ultimate outcome, however, was unaltered. With the exception of the transitory periods of fall in temperature, lasting a few days, the remaining cases were unimproved by treatment. Two patients were alive and still under treatment. The periods since the onset of their illness were four and eight months respectively. (Cases 14 and 15, chart 2.) Both cases continued to show both fever and splenomegaly at the time of publication.

Effect on Bacteremia. All cases on whom blood cultures were drawn during treatment revealed a growth of organisms. This is at variance with the work of Spink and Crago [8] who reported temporary sterilization of the blood in 6 of 12 cases treated with sulfanilamide. All the cases in this group that revealed a growth of organisms on culture before treatment, also revealed growth during treatment. The presence of sulfanilamide and its derivatives in the blood in therapeutic concentrations, therefore, did not render it sterile.

Case 10 revealed no growth at any stage of the disease, yet at postmortem, typical vegetations were found. Blood cultures from case 11 revealed a growth of *Diplococcus pneumoniae* following an attack of bronchopneumonia. This organism was resistant to sulfanilamide therapy.

Pathological Findings. Seven of the 11 fatal cases were examined postmortem, and at autopsy revealed typical vegetations, all with bacteria incarcerated beneath a fibrinous covering. In six of seven cases the spleen was enlarged, varying in weight from 290 to 610 gm., and presented the pulpy, soft appearance associated with septic states. Numerous infarcts were also noted in the spleen, kidneys, lungs and liver.

Comment

The problem presented in the treatment of infectious endocarditis by means of chemotherapy concerns itself in large part with the susceptibility of the causative organisms to the type of chemotherapy chosen. Experimental proof of the importance of the strain of organisms found, in determining the response to sulfanilamide and its derivatives, is given by the work of Swain [18] who found that *Streptococcus viridans* organisms isolated from two cases resistant to treatment with sulfonamide compounds were not inhibited by sulfanilamide, sulfapyridine or diaminosulfone in vitro. From the blood of two other cases which had a temporary remission with treatment, strains of *Streptococcus viridans* were isolated which were inhibited in growth in vitro. Osgood, Brownlee and Joski [19] also found with in vitro experiments, that some groups of *Streptococcus viridans* were resistant to sulfapyridine, sulfathiazole and sulfamethylthiazole, while the growth of other groups was inhibited. Similarly, working with sulfanilamide in vitro, Bliss, Long and Feinstone [20] found 42 of 45 strains of *Streptococcus viridans* were inhibited in growth by the addition of sulfanilamide, while the remaining three strains were unaffected. The response to sulfanilamide compounds of the beta hemolytic streptococcus is well known; this may account for the success of treatment in case 2 (chart 1) treated by Hussey [4] and in case 18 treated by Alexander,[16] the beta hemolytic streptococcus being causative in each instance. Relative resistance of the pneumococcus to treatment with sulfanilamide has been noted by Long and Bliss,[1] and this is in accord with the fatal outcome in case 12 of this series (chart 2) where the pneumococcus was grown from the blood. Failure of sulfanilamide and sulfapyridine to cure pneumococcal endocarditis, has been previously noted by Terry,[21] Fishkin,[22] and Hollander.[23]

The assumption, therefore, that patient 8 who recovered and patient 13 who was markedly improved, were infected with strains of organisms susceptible to the drugs used, seems likely.

The cause for the fall in temperature in the fatal cases which occurred during the administration of sulfapyridine and sulfathiazole, and to a lesser extent with sulfanilamide, has recently been clarified. Clinical observations on the depression of temperature in infectious endocarditis which occurred following the administration of sulfapyridine, have been made by Whitby,[24] Ellis,[25] Ravina [26] and Jones.[27] The latter author noted a fall of the temperature to 94.0° during treatment with this drug. Beeson and Jane-

way [28] were able to demonstrate a fall of temperature below normal in rabbits after the administration of sulfapyridine. Lesser depressions were found with sulfathiazole and sulfanilamide. Fever produced in these animals by typhoid vaccine given intravenously was quickly abolished by sulfapyridine but not by sulfathiazole.

In cured cases the fall in temperature would seem to be due to sterilization of the blood stream and eradication of the infection. In the 11 fatal cases in this series, the blood was not sterilized; yet a fall in fever occurred in most cases. One may conclude that the temporary depression in temperature noted was in part due to the antipyretic action of the drugs used. Other investigators,[8] however, have noted a temporary sterilization of the blood, and in these patients the fall in fever may be accounted for by control of the infection.

The incarcerated bacteria in the vegetations of subacute endocarditis remain as the major obstacle to treatment. Septicemia, due to streptococci without a complicating vegetative endocarditis, is capable of cure by chemotherapy.[29, 30] It is believed that in case 13 the cure was accomplished or the disease aborted because the growth on the valves had not had an opportunity to accumulate significant fibrinous vegetations. When fibrinous material has appeared on the heart valves, cure is much more difficult. Kelson and White [10] have reported three cases (numbers 10, 11, 12, chart 1) cured by heparin in conjunction with sulfapyridine. Friedman, Hamburger and Katz,[31] Witts [32] and Kleiber [33] have reported cases of subacute bacterial endocarditis unsuccessfully treated with heparin and sulfapyridine. Duncan and Faulkner [34] have demonstrated that the penetration of sulfapyridine and sulfanilamide, sulfathiazole and sulfamethylthiazole, into a previously formed clot was negligible. However, when these drugs were added to the blood before clotting occurred, a considerable amount of the drugs was found in the clot. Hence, if treatment is instituted very early in the disease, as the clot is forming, the possibility of destruction of organisms in the vegetation would seem likely. This would seem to have occurred in case 13.

From the work of Libman,[35] Capps [36] and Welch,[37] it is evident that spontaneous cure with healing of the vegetations may rarely occur. In assessing any cure, furthermore, a prolonged period of observation is necessary. Case 8 of the present group (chart 2) has been observed for two years and nine months following the beginning of treatment without relapse. This is a longer period of observation before report of a cure of subacute bacterial endocarditis (following treatment with sulfanilamide), than any that has previously appeared in the literature.

It is our belief that treatment with sulfanilamide and related compounds should be begun as soon as the diagnosis is made, and continued as long as possible. When no clinical improvement occurs with one of the sulfonamide compounds (as in case 13) another should be given a trial. With this form of therapy a minority of the cases will show improvement or cure, but this

fortunate group can be found only by clinical trial. With the remaining fatal group, remissions in some cases of varying length will probably occur.

Summary

1. The clinical course of 15 cases of subacute bacterial endocarditis treated with sulfanilamide, sulfathiazole and sulfapyridine has been reviewed.

2. One of the cases has been cured and is alive and well two years and nine months after treatment was begun. A second case is alive at the time of writing, five months after the onset of illness, and has been apparently cured.

3. A collection of 31 previously reported cases of subacute endocarditis cured by sulfanilamide and its derivatives, has been gathered from the literature.

4. The use of sulfanilamide, sulfathiazole or sulfapyridine in all cases of subacute endocarditis seems warranted. Theoretically, the earlier the treatment is instituted, the better the chances are for cure.

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THE AMERICAN BOARD OF INTERNAL MEDICINE AS A FACTOR IN SCHOLARSHIP IN AMERICAN MEDICINE*

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It is now five years since the American Board of Internal Medicine was organized. In this period a total of 2,449 have been certified, 624 of these by examination. It is perhaps salutary again to review the objectives of such certification as the Board conceives them, and to look ahead to anticipate, if possible, some of the requirements of the medical leaders of the coming years. The Board recognizes that it is only one of the agencies concerned in efforts to improve the quality of medical care and scholarship. All those who participate in programs of graduate education, whether in preparation for certification by the various boards, or under other auspices, state or local, do so voluntarily, and the programs are designed to meet the needs and abilities of the several categories of physicians. The years of preparation for examination for certification are years of growth and of further development of orderly and thorough habits of study and thought. The examination is a necessary method of determining whether candidates have attained a degree of medical information and experience likely to ensure their future continued growth in medical knowledge and scholarship.

Much concern has been expressed over the large proportion of graduates in medicine who are seeking to become specialists, but already in some sections there is evidence that the trend of medical graduates is increasingly toward general practice. Realization of the expenditure of time and effort necessary to qualify the physician in a specialty is also likely to limit the number of candidates to those who are willing to work hard and long, and who in addition feel the urge to excel in some field of medicine. However, there always will be need for physicians with additional training in the more specialized branches of medicine. It is the task of the Boards to see to it that those who enter the specialties with their approval, shall be fully qualified.

While there are a number of incidental aims and satisfactions for the candidate which derive from the passing of the examinations, such as the completion of one of the qualifications for membership in the College of Physicians, the personal sense of satisfaction of having passed a milestone in one's career, or the attainment of a measure of approbation of one's colleagues, the Board is more interested in the fact that the candidate has embarked on a career of study voluntarily, and has thereby expressed the desire to excel, and to participate personally in the world's progress in medicine.

The successful student of the future, as in the past, must have good health, good principles, good tools, and the will to work. The quality of

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the student's training in secondary school and college has much to do with supplying him with effective tools for his medical studies. A sound classical education, which at the moment seems to be a little out of style, should supply him with usable tools in Latin, French, German and Spanish, and, most important, a knowledge of English grammar and ability easily to express his thoughts in good English. Chancellor Carmichael of Vanderbilt University in discussing the contribution of liberal education to professional studies has reëmphasized the importance of sound fundamental education as a preparation for successful prosecution of later professional training. Some knowledge of Latin and Greek is necessary to understand terms, and of French and German for access to the literature of the more recent past and present. Foreign language study gives the American student a knowledge of his own language, a precision of expression, and hence precision of thought. These educational acquisitions are more important at the preparatory college level than is factual learning, and provide the attitude of mind, and the perspective sense of values essential to him who aspires to achieve real success in a learned profession.

I am aware that it may appear unseemly for a physician to voice criticism of certain current educational methods practiced in some colleges and secondary schools. But contacts with a considerable number of earnest and industrious medical students, and with young ambitious physicians, as well as experiences in the examinations of the Board, lead to the conclusion that in many instances the evident scholastic deficiencies are not due entirely to lack of industry or of professional guidance, but to faults in early education in secondary schools. No doubt great improvement has been made in methods of teaching a number of the subjects in the curriculum of secondary schools, but judging from results the teaching of English has shared least in this improvement.

In a recent discussion of the use of texts in High Schools it was stated that in the High Schools of one large city, 20 per cent of the children admitted from the grade schools had not sufficient command of English to be able to read and understand the material set forth in the High School texts. It may be argued, of course, that the great masses of children in public schools make it impossible to insist on much more than a rudimentary knowledge of reading, writing, and arithmetic. But the same conditions of superficial teaching of English exist in many private elementary and secondary schools. The recognized achievements of "Progressive Education" do not seem to have included thorough drill in the elements of English. Ability to think is made effective by ability accurately to express one's thoughts. "Usage" is but a poor substitute for an early and thorough analytical study of grammar and sentence structure. The student of medicine, thus ill prepared, manages to limp through such English as he is obliged to take in college. Later in the medical school, he wonders why at examination time his instructors fail to appreciate his efforts to demonstrate his knowledge in writing.

No matter what form of practice the medical student aspires to, he needs a basically sound preliminary education. A good general knowledge of world history will stabilize his fundamental thinking. The mental training afforded by mathematics, and a sound knowledge of the sciences, especially physics, chemistry, and biology, will make much easier the difficult and crowded years of his medical course, and later will sharpen his critical sense in the evaluation of medical problems and conclusions.

The secondary school and college preparation of medical students, as indeed that of all students entering professional careers, varies widely in quality. Those students whose early preparation is defective may still recover lost ground, and reach high attainments later, but this will be only at the expense of time and greater effort when all their energies should be directed toward the mastery of the medical curriculum.

General medical education is now much more uniform in quality than is secondary and college education, but even in medical education there is great divergence in the qualities of preparation of students and in the inspiration offered by the several schools. And even if schools were all on a par, there would still be a wide variation in quality of performance of individual students. Medical students like other people have differing mental endowments and differing ideals and personalities. The requirements in the practice of medicine, beyond the minimum standards for licensure and the safe care of the sick, vary according to locality and the type of work to be undertaken. The American Board is primarily interested in encouraging men to go further educationally than the minimum legal requirements. Such additional training should not unfit them for the practice of medicine, but should make them better, safer doctors, whose medical life will be brightened by the pleasure of participating in the advances and the scholarship of medicine. From such a group must come the qualified leaders of the future.

The necessity of research in medicine is self evident. Vast sums are devoted to the promotion of a multitude of projects. Some of this effort is barren, but now and then a new fact, or method, or principle, is established which justifies the entire expenditure. Some of this research is carried on by men who are well prepared also in clinical medicine. Other equally important and sometimes more fundamental research is carried on in internal medicine by men whose progress would be impeded rather than helped by insistence that they acquire also the degree of clinical experience demanded of candidates for the American Board of Internal Medicine. For such specially endowed research minds, other scholastic goals and rewards are available. The field of the Board of Internal Medicine is thus not all-inclusive.

The Board deplores the tendency of some of the younger men to regard the successful passing of the Board's examination as an end in itself rather than as an indication of the acquirement of another section of preparation for a life work. Out of this misconception of the ultimate aims of the Board come several rather unfortunate attitudes of medical students. In-

ternships in hospitals are of various lengths and content of experience arranged to suit the peculiar needs and available facilities of hospitals, and in some cases to comply with state laws. Many of the better hospitals hold that a rotating internship of one year affords but a smattering of experience, and that to be effective for the hospital and especially for the intern who contemplates general practice, a rotating internship should be at least two years in duration. While the internship may repair mistakes and fill gaps left by an inadequate medical curriculum, this is not its primary purpose. Rather should it be regarded as affording a period of growth in an orderly program of continuing education. If the service offered is confined to fewer departments of medicine, an adequate intern experience may be acquired in a somewhat shorter time. The prospective intern, however, feels that he must get on with his formal preparation for the Board and desires to cut his internship to the minimum one year, so that he may proceed with his residency, forgetting that what he needs is experience, which may be as well or frequently better attained in the two year internship than in some short internships and residencies. The attempt thus to save time and to come up for examination in the minimum allowable period may result in an inferior preparation, and in some cases failure of the candidate.

Further it is difficult to see how coaching in the ordinary sense can be of any material benefit to the candidate. Preparation must be based on years of continuous thoughtful study free from the inhibitions of stereotyped questions, or of conformity to any one rigid program of training. The questions asked by the Board are designed to determine whether the candidate has a broad knowledge of the fundamental facts of medicine. It is evident that the few questions asked can afford only a sampling of this knowledge. Some questions have been criticized as being of the nature of catch questions, or questions which stray from the beaten path of information in common use. The employment of an occasional question of this kind has been deliberate and purposeful, in order to explore the extent of the candidate's collateral information. Final judgment is based not on one question but on his general ability and knowledge as demonstrated by the examination as a whole.

The young physician has already spent at least eight years in his preparation for medical practice. How can the suggestion for another five year minimum of preparation be justified? Viewed as a requirement for practice it evidently cannot be justified, either legally or economically. The first eight years are required in satisfaction of the demands of the police power of the State. Anything further is entirely voluntary on the part of the physician. The justification therefore must come from the physician's own willingness to work, in order to acquire a superior knowledge of his subject, and in his hope that he may contribute something to the sum of human knowledge, or that in any case he may have the satisfaction of superior accomplishment in the care of the sick. Many excellent and able physicians quite properly will not feel that they can, or should, devote further time to

formal study. Others will desire to obtain additional preparation, and for these, certain suggestions as to residencies, supplementary study in the basic medical sciences, or the less formal but frequently effective preceptorship are offered. The American Board believes that such programs, or similar ones, will be useful guides to perhaps the majority of candidates, although the Board recognizes that other plans may be equally effective. The test of any program will be the results achieved by the candidate. In outlining such programs for those who wish advice, the Board hopes to assist the candidate to avoid inferior and superficial plans which may lead to failure and disappointment in later years, at a time when the golden opportunity for growth is past.

Just as candidates voluntarily apply to the Boards for examination, so the Boards themselves are voluntary in their organization and should restrict their activities to the setting and maintenance of standards. Any pronouncement by the special Boards, suggesting that their certificates be made a requirement for membership on hospital staffs is to be deprecated. Such a pronouncement would interfere seriously with the influence of the Boards in promoting medical scholarship. If hospitals, or other civic or state organizations, see fit to utilize the information as to standards of professional ability afforded by certificates of the Boards, that is a matter of their local policy. It should never be imposed on them by the Boards. The function of the Boards is to establish standards of achievement. By the nature of their organization, they have no authority, nor were they intended to have power, to enforce their standards on anyone.

The physician's choice of his career in medicine will depend on his inclination, his ability, his opportunity, and his preparation. His preparation, including his premedical education, will influence his inclination, and if faulty, will limit the opportunity to which his ability might otherwise entitle him. Habits of thoroughness and the willingness to work are essential.

Into whatever sphere of medicine he enters, the effective doctor should maintain a scientific attitude toward disease, and at the same time that of humanity toward the patient. The science of medicine must be combined with a large element of human sympathy and understanding; as Morgagni put it—the resolve " to be useful to mankind."

CASE REPORTS

HISTOPLASMOSIS OF DARLING; REPORT OF A CASE*

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Histoplasmosis is a rare, anatomically widely disseminated, usually fatal fungus infection often characterized by fever, anemia, leukopenia and splenomegaly. The condition is caused by *Histoplasma capsulatum* which may be found in large numbers in the reticulo-endothelial cells and may be cultivated from the blood and other tissues. No specific therapy has been found. Mantell et al., as reported by Meleney,[1] used a pentavalent antimony preparation (Neostam) possibly with some success.

The fungus, *H. capsulatum*, has two forms. One is yeast-like and occurs in the blood and reticulo-endothelial cells. The other, the mycelial form, is assumed when it is grown outside the body. This fungus has been well described by DeMonbreun.[2]

Blood cultures in infusion broth incubated at 37° C. show both types. When such cultures are plated out on blood agar and kept sealed at 37° C. colonies of both forms will develop. On blood dextrose agar plates made from the patient only the mycelial type of colony has been described.

The mycelial form alone grows on cultures held at room temperature. Its development is enhanced by the use of media adjusted to a pH of 6.5 with hydrochloric acid. The growth is white and cotton-like. Numerous aerial hyphae develop. The mycelia are highly refractile, straight, branched and segmented. Aerial spores 10 to 25 microns in diameter (as shown in figures 1 and 2) appear about the end of one week.

On blood agar the colonies of the mycelial type usually do not show aerial hyphae. They are reddish-brown and blend with the surrounding media.

The yeast-like form grows only on blood or serum agar at 37° C. The colonies are brownish-white, elevated, round and resemble those of bacteria. In young cultures the organism is oval and approximately 3 to 3.5 microns in diameter. Budding is often seen. The individual cells possess a thin membrane which surrounds a cytoplasm containing one or more fat droplets and often a protoplasmic granule in active Brownian movement. The cell tends to be partially decolorized by Gram's method.

The fungus has never been found outside the animal body and has only been isolated from man and the dog.[3]

When injected into suitable animals the mycelial form causes an abscess from which the yeast-like type can be cultivated on blood agar. If this latter form is injected intravenously lesions develop similar to those described in man.

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TABLE I

Author	Year	Place	Positive Cultures	Organism Found in Blood Smears	Organism Found in Biopsies	Organism Found at Autopsy in							
						Lung	Liver	Spleen	Nodes	Adrenals	Intestine	Marrow	Various Organs
Clemens and Barnes	Sept. 1938	Ky.	Blood			+	+	+	+				
Dodd and Tompkins	1932	Tenn.	Blood	+		+	+	+	+		+	+	
Forry and Cumbertson by Meleney		Ind.	Biopsy and blood		+						+		Viscera
Hansmann and Schenken	1934	D. C.	Skin ulcers		+	+			+	+			Skin
Reid, Scherer and Irving	1939	Va.	Blood	+	+	+	+	+	+		+	+	Kidney
Wright and Hachtel	Feb. 1938	Md.	Blood		+	+	+	+	+				
Agress and Gray [17]	1939	Mo.				+	+	+	+		+		Heart and nasal septum
Almeida and Lacaz	1939	Brazil	Skin		+								
Amolsch and Wax [18]	1939	Ohio		+	+								
Crumrine and Kessel [19]	1931	Calif.				+	+	+	+		+		
Darling	1906	C. Z.				+	+	+	+				
Darling	1908	C. Z.					+	+	+				
Darling	1908	Pan.				+	+	+	+		+		
Gunter and Lafferty [20]	1940	Ala.				+	+	+	+				
Humphrey	1940	Mich.					+	+	+				Heart, pancreas, kidney
Humphrey	1940	Mich.			+	+	+	+	+				Kidney
Mantell et al. by Meleney	1940	Fla.			+								

TABLE I—*Continued*

Author	Year	Place	Positive Cultures	Organism Found in Blood Smears	Organism Found in Biopsies	Organism Found at Autopsy in							
						Lung	Liver	Spleen	Nodes	Adrenals	Intestine	Marrow	Various Organs
Martin and Silber by Meleney [1]		Calif.				+	+			+			
Meleney	1939	Tenn.				+							
Meleney	1939	Tenn.				+	+	+					
Moore and Blanche by Meleney [1]		Mo.				+							Prostate
Müller [21]	1939	Java							+		+		
Negroni	1940	Arg.	Skin ulcer										
Parsons by Meleney [1]		Mich.								+			
Parsons	1940	Mich.	Nose ulcer										
Phelps and Mallory	1926	Hon.				+							
Riley and Watson [22]	1926	Minn.				+	+	+	+				
Shaffer, Shaul and Mitchell [23]	1939	Va.					+	+	+	+	+	+	
Villela and Para by Meleney [1]	1940	Brazil					+						
Wade by Meleney [1]	1926	P. I.											Skin, viscera
Weller by Meleney [1]		Ohio			+								
Williams and Cromartie	1940	Tenn.							+				Pharyngeal ulcer and epiglottis

Thirty-one cases of histoplasmosis have been found in the literature. Darling [4, 5, 6] reported three cases and Humphrey [7] two. Meleney [1] collected 11 previously unpublished cases and added two of his own. The others have been reported singly.

Among the 31 cases reported (table 1) there have been 24 autopsies. In a few of the postmortems the organism was not widespread. Phelps and Mallory [8] found it in the air passages only. The case of Parsons reported by Meleney [1] showed "Histoplasma-like" organisms in one adrenal in a patient with generalized tuberculosis. In a case of leukemia reported by Williams and Cromartie [9] it was found in pharyngeal ulcers, the epiglottis and cervical nodes. In one instance Meleney found the fungus only in the lungs.

H. capsulatum has been isolated in culture in eight cases. In two instances (Parsons [10] and Negroni [11] the organism was obtained from ulcers alone and no information as to the outcome is available. Hansmann and Schenken [12] grew the fungus in the antemortem cultures of cutaneous ulcers and then found it in the tissues both at biopsy and necropsy. They classified this organism as belonging to the genus *Sepidonium*. Most writers since have considered this case as histoplasmosis. DeAlmeida and Lacaz [13] cultivated the fungus from a biopsy of the skin and found the organism in sections. The four remaining cases (Dodd and Tompkins [14]; Forry as reported by Meleney [1]; Clemens and Barnes [15] and Reid et al.[16] had positive blood cultures and exhibited the parasites in many organs at autopsy. To the present total of five cases from which *H. capsulatum* was isolated and later found disseminated in the organs at necropsy the writers wish to add another.

Case Report

The patient, a white male, bartender, 59 years old, was last admitted to St. Joseph's Hospital on the service of Dr. E. H. Benson, February 9, 1939. He had had two previous admissions, April 30, 1936 and April 11, 1937. During the patient's first hospital stay it was found that he had diabetes mellitus which was treated by diet and insulin in the usual manner and he was discharged after 17 days. His second admission was because of an extensive suppurative process in the calf of the left leg. Incision liberated much pus from which a staphylococcus was isolated. The diabetes mellitus was controlled by diet and insulin and he was discharged after 33 days. Three weeks prior to the last admission he had had attacks of sharp grinding epigastric pain which was worse after a meat meal. Some relief was obtained by belching gas. There was no nausea or vomiting. During the three weeks he had had a hacking cough, night sweats followed by chills and a constant frontal headache. Examination revealed an emaciated, febrile, very ill man. The skin presented a distinct icteric tint. His heart was rapid. No abdominal tenderness or rigidity was elicited but a mass was felt in the region of the gall-bladder. The second toe of the left foot was discolored and appeared partly gangrenous.

Laboratory: Blood Wassermann, negative.

Blood counts:	2/9/38	2/10/38	3/2/38
Hemoglobin	65%		72%
White blood cells	2,500	4,850	2,500
Red blood cells	4,250,000		4,300,000
Polymorphonuclear	75%		74%
Lymphocytes	23%		26%
Mononuclear	2%		

Icteric Index: 2/17/38—3; 3/4/38—12.

FIG. 1. Colony showing aerial hyphae bearing numerous aerial spores. × 150.

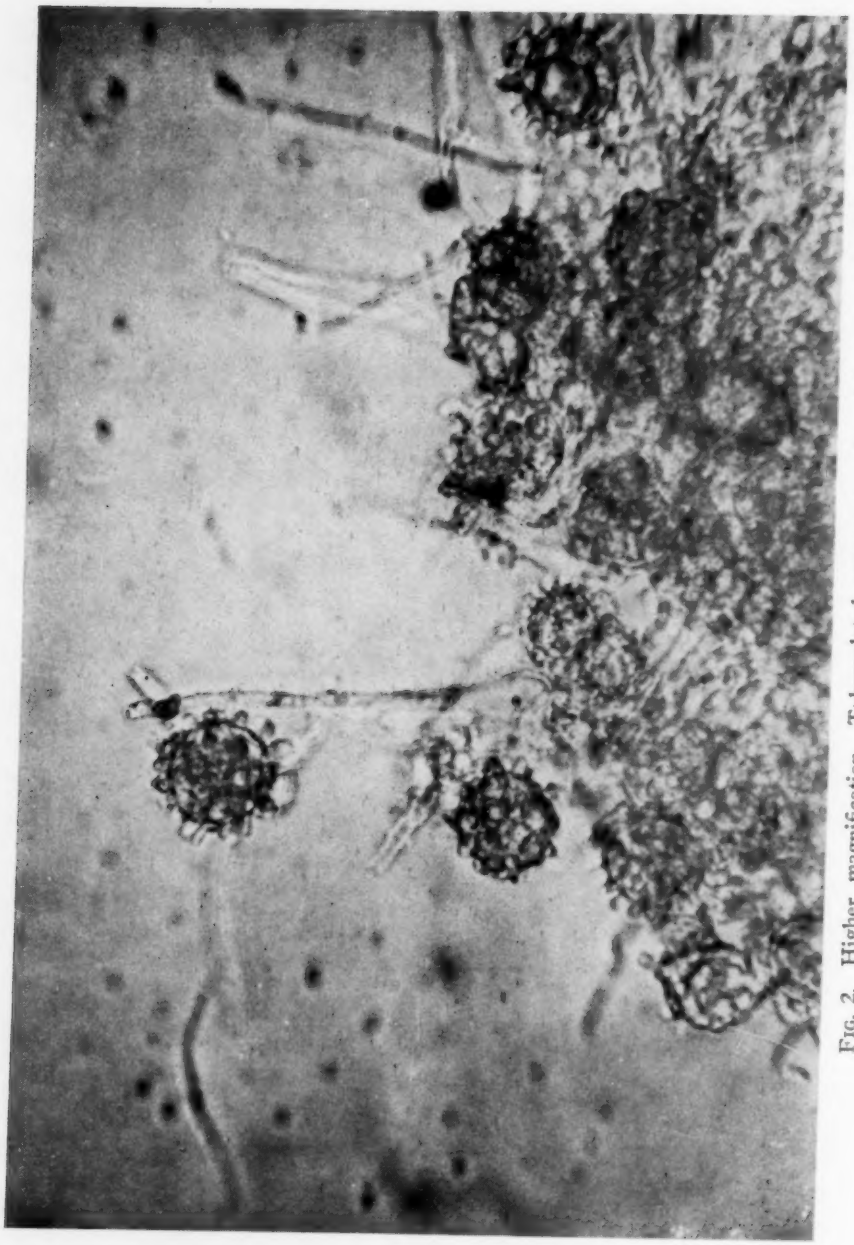

FIG. 2. Higher magnification. Tuberculated appearance of aerial spores. × 930.

Blood non-protein nitrogen was normal. There was marked variation in blood sugar. On a constant diet and insulin dosage it varied from 105 to 190 mg. per cent.

Serum agglutination for typhoid, paratyphoid, tularemia and undulant fever was negative.

A gastrointestinal examination by roentgen-ray failed to reveal any significant lesions.

By roentgen-ray the gall-bladder was considered pathological. Roentgen-ray of the chest was interpreted as showing bronchitis.

The patient ran a septic course with fever ranging from 95° to 103° F. There were frequent sweats and the diabetes was hard to control.

On March 14, 1938 an exploratory abdominal operation was done under local anesthesia. The liver was found to be nodular. The head of the pancreas and the regional nodes were hard and nodular. A node was removed for examination. The patient became weaker, temperature was below normal, pulse was rapid, skin clammy, urine contained sugar when the blood sugar was 125 mg. per cent.

The lymph node was 2 cm. in diameter and had a homogeneous gray, opaque cut surface. Sections showed its architecture to be greatly altered by large areas of necrosis surrounded by a thick zone of conspicuous phagocytic cells containing as many as 25 bodies 3 to 4 microns in diameter. The bodies had a small basic staining central portion around which there was a clear zone. Each organism had a sharp margin which strongly suggested a capsule.

The section of the lymph node was interpreted as histoplasmosis and led to the taking of blood cultures on March 17 and 18. The patient died on March 19, 1938. The organism (figures 1 and 2) developed in the cultures after five days' incubation and was found to be morphologically like that described by DeMonbreun.

At autopsy the body was examined by a member of the house staff who stated that it was emaciated and presented a recent right rectus wound held together by silk sutures. There were many pleural adhesions but no fluid in the pleural sacs. The lungs were soft and contained many small focal lesions suggestive of tubercles. The spleen weighed 500 grams and contained many isolated gray nodules 2 mm. in diameter. The liver was pale and weighed 3000 grams. Its capsule was smooth and had a gray color mottled by pale brown. The lobular markings were not evident on the cut surface which presented an appearance similar to that seen through the capsule. The kidneys weighed 250 grams each. They had granular surfaces after the capsules were removed. The cortex and pyramids showed no definite abnormality. The gall-bladder and stomach showed no significant abnormality. Unfortunately the pancreas was not examined.

Section of the lung shows marked distortion of the alveolar architecture near the pleura by fibrous tissue. There are irregular spaces which contain a papillomatous structure covered by columnar epithelium. The abnormal tissue described above can be followed to the pleura where there is a marked deposit of granulation tissue in which one finds many lymphocytes and large phagocytic cells containing organisms morphologically like those described above. In the deeper pulmonary tissues there are sometimes found clumps of large apparently phagocytic cells but in no instance do they contain the organisms which are so numerous in the pleural zone. In the spleen there are frequent areas of necrosis around which large cells containing bodies similar to those seen in the lymph nodes and pleura are found in moderate numbers. The organisms do not appear as numerous in the spleen as in the lymph node. The portal zones of the hepatic lobules are very large and tend to have a sharp margin. They contain considerable fibrous tissue and lymphocytes as well as many large cells similar to those seen in the lymph node. In most of the lobules the only organisms found are in the portal zones. In a few places actual necrosis is found. Here there are many more parasite-laden cells immediately around the necrotic tissue. These cells can be fol-

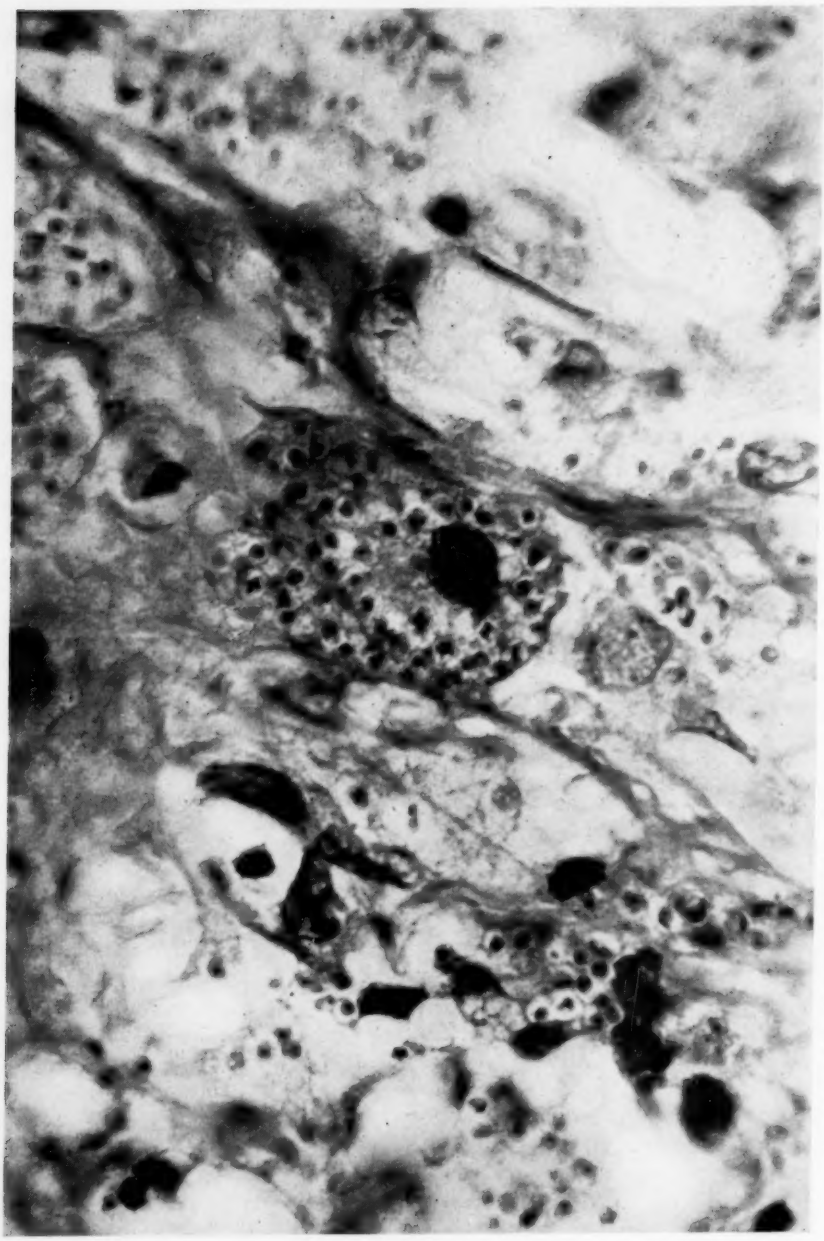

FIG. 3. Oil immersion. Large mononuclear cells in a lymph node. There are innumerable parasites.

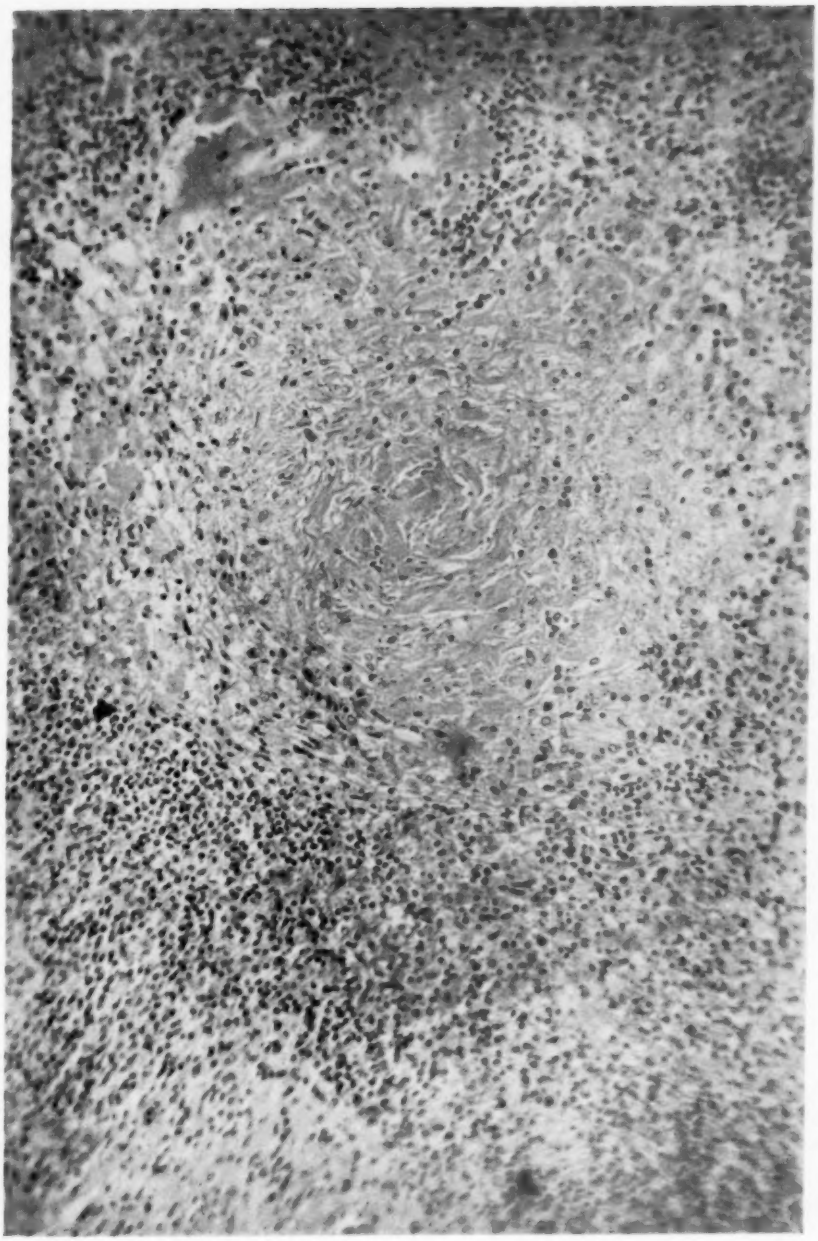

FIG. 4. Spleen. A focal area of necrosis around which large cells containing organisms can be seen.

lowed for some distance in the blood sinuses around these necrotic areas. No organisms can be found in the sinuses except near the portal areas and areas of necrosis. Sections of the heart and kidneys failed to show any organisms or other significant lesions.

The usual hematoxylin and eosin stain after formaldehyde fixation showed the intracellular forms better than Gram's stain (MacCallum's method), Giemsa's stain or acid fast stain.

The mycelial form of these organisms obtained from blood cultures of the patient was injected subcutaneously in a Rhesus monkey. An abscess developed at the site. This was aspirated and cultured on blood agar at 37° C. Then the yeast-like form thus obtained was injected into the veins of a second monkey. The second monkey became ill but after several months seemed to recover. During his illness blood cultures showed *H. capsulatum*. After months he was killed and at autopsy many small old abscesses were found in the lungs. These abscesses had purulent centers and a fairly definite fibrous tissue wall. No organisms could be demonstrated at autopsy either by sections or cultures. Further study of the pathogenicity of this organism is contemplated.

Summary

1. A case of histoplasmosis in a bartender and diabetic is reported. This is the second case in which the diagnosis was made before death.

2. The diagnosis can be made only by finding the organisms in stained smears or sections or by cultures. It may be suspected in a case of continued fever, anemia, splenomegaly and leukopenia.

3. The organism will grow in ordinary nutrient broth or on blood agar. It requires at least five days to develop.

4. Tissues fixed in formaldehyde and stained by hematoxylin and eosin show the intracellular form of the fungus well.

5. The yeast-like form was injected into a Rhesus monkey and several times *H. capsulatum* was obtained from the blood stream of the monkey. The animal recovered and at autopsy no organism could be found.

6. The disease may not be generalized and does not appear to be always fatal. Treatment by pentavalent antimony is mentioned by Meleney.

The authors wish to express their gratitude to Dr. E. H. Benson for permission to report this case.

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LATE TULAREMIC SEPTICEMIA: RECOVERY FOLLOWING ADMINISTRATION OF SULFANILAMIDE COMPOUNDS *

By LESTER M. MAY, M.D., *San Antonio, Texas*

TULAREMIA is an increasingly common disease, carrying with it, in severe cases, a definite mortality. Curtis [1] has reported on the use of sulfanilamide in tularemia. The following case represents another and somewhat earlier usage of sulfanilamide compounds.[2] The case is of further interest in that it displayed several unusual diagnostic features. The clinical course was rather more severe than in Curtis' case, while the recovery following specific drug therapy was quite as rapid and as definite.

CASE REPORT

M. M., a white male aged 21 years, was admitted to the Sinai Hospital December 9, 1936 in a semi-comatose state. He was employed in the kitchen of a local hotel as chief poultry and game dresser. Rubber gloves were not worn in this work. One year before, another kitchen employee had contracted what was diagnosed as "rabbit fever." Six days before admission, the patient had skinned and quartered six rabbits, but did not cut or bruise himself in so doing. Three days before admission, he went to bed feeling well, but awoke suddenly with violent shaking chills. Severe and almost constant frontal headache, generalized aching, and ten shaking chills occurred within the next 24 hours. This same day, he noted that the entire terminal phalanx of the third finger of the left hand was painful, reddened, swollen and tender. Seven shaking chills occurred on the day before admission. Sore throat, an occasional dry cough, and a localized area of pain, tenderness and swelling in the left axilla were noted this same day. On the evening before admission, the inflammation of the third terminal phalanx appeared to subside, but the terminal phalanx of the fourth (ring) finger of the left hand now began to show similar inflammatory changes. The patient vomited and had a rather copious epistaxis on the morning of admission. No other skin lesions of any sort had been noted.

On admission, he appeared acutely ill, and was occasionally disoriented and incoherent. The temperature was 105° F., the pulse 105, the respiratory rate 26. The blood pressure was 110 systolic, 80 diastolic. Several shaking chills occurred during the examination. The terminal phalanges of the third and fourth fingers of the left hand were tender, red and swollen; there were no skin abrasions or ulcerations, nor were any other dermal lesions visible. In the left axilla a firm, smooth, exquisitely tender acorn-size lymph node was palpated. There were a few shotty, non-tender nodes at the jaw angles, but no other palpable nodes. The eyes were clear externally. A small amount of dried blood was present just within the nares, and the upper nasopharynx contained several large masses of dried blood. The lower pharynx was moderately and diffusely reddened. A few coarse rhonchi were heard in both interscapular regions after cough; the lungs were otherwise clear to percussion and auscultation. The splenic edge was felt at the left costal margin. The neck was held slightly extended. Babinski's sign on the right was equivocally positive.

Admission laboratory findings revealed hemoglobin 88 per cent, erythrocytes 4,800,000, and leukocytes 12,000; polymorphonuclears 80 per cent, lymphocytes 18 per cent, monocytes 2 per cent. The examination of the urine was negative. A throat

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From the Medical Service of Dr. Charles R. Austrian, Physician-in-Chief, Sinai Hospital, Baltimore.
The drugs used in this case were Prontylin and Prontosil, supplied by the Winthrop Chemical Co., New York City.

swab showed no pneumococci. Spinal fluid drawn on admission was found to be under normal pressure and clear; the Pandy test was negative; 8 mononuclear cells were found; and a culture proved negative. Blood culture, taken on admission, and cultivated on routine blood agar media, showed no growth. A blood Wassermann test was negative, and blood sugar and blood urea levels were within normal limits. Admission roentgen-ray of the chest was interpreted as normal.

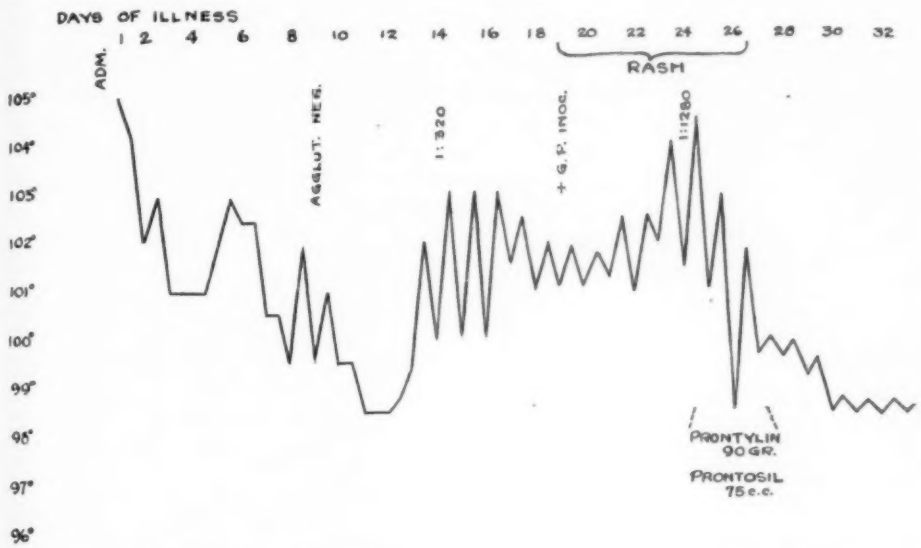

CHART 1. Temperature graph indicating rapid termination of septic curve following institution of drug therapy.

The inflammatory swelling of the two terminal phalanges, as well as the swelling of the axillary node, subsided completely within the first few days. The spleen was not palpable two days after admission. Repeated blood cultures were taken, and inoculated on routine blood-agar media; all showed no growth. The lungs remained clear. He soon became better oriented, but still appeared rather toxic during the first week. Agglutinations on December 18 were negative as well as those performed on admission. Agglutinations on December 23 were positive for *B. tularense* in 1:320 dilution. Temperature and pulse fell to normal by slow lysis, and the general condition gradually and markedly improved. However, on December 21 a secondary intermittent fever began and persisted, spiking daily to 102–103° F. At the same time, he again appeared quite ill showing the general signs of toxicity and impaired sensorium seen on admission, although in slightly less degree. On December 28, a peculiar blotchy rash appeared over the tibiae, patellae, and elbows—erythematous and quite symmetrical. This rash became tender on the next day, and subsided completely by January 5. On the day of the rash's first appearance, a guinea-pig was inoculated with freshly-drawn blood, and showed signs of tularemia five days later—conjunctivitis, lymph node enlargement, and smears positive for *B. tularense* from conjunctival fluid and urine. By January 2, the patient's blood titer for *B. tularense* had reached 1:1280.

On January 2, treatment was started with Prontylin gr. 5 every 3 hours, and 5 c.c. Prontosil solution every four hours intramuscularly. A total dosage of 90 gr. of Prontylin and 75 c.c. of Prontosil was given over a three day period. A dramatic drop in temperature occurred on the second day—the first fall in 12 days. A secondary rise occurred that night, but the temperature came down and remained down

for the rest of the hospital stay. Prontylin dosage was increased to gr. 15 every 4 hours on January 3. Treatment with Prontylin and Prontosil was discontinued on January 5.

During the entire stay in the hospital, the urine remained clear, and the leukocytes ranged between 9000 and 12,000, averaging 70 per cent polymorphonuclears, and 30 per cent lymphocytes. He was discharged afebrile and cured on January 24.

Comment

Francis [2] states that a satisfactory and successful method for obtaining laboratory evidence of blood stream invasion by *B. tularense* is to inoculate guinea-pigs with blood taken from patients during the first to twelfth days of the illness. The guinea-pig is then examined for evidences of tularemia, or its tissues are inoculated on artificial media containing cystine. In a review of the literature, he reports on 52 cases in which guinea-pig inoculation was positive for *B. tularense*. Of these, five positive inoculations came from blood drawn during life. He states: "Blood taken during life, after the first week of illness, was always negative except that one case yielded a (positive) culture on the twelfth day." Hitch and Smith,[3] in a comprehensive review, comment that bacteremia in tularemia always ceases by the fourteenth day. They state "Repeated inoculations of guinea-pigs with patients' blood have never given positive results later than this." Therefore, the septicemia in this case must be regarded as occurring at, or persisting to, an unusually late date, since a positive blood inoculation was here obtained on the twenty-second day of the illness.

The primary lesion in this case, a diffuse inflammatory cellulitis of two adjacent terminal phalanges, was also distinctly unusual. The clinical duration was only five days. Perret,[4] in a clinical review of 69 cases, describes the primary lesion of the "ulcero-glandular" type of tularemia as being a "small, superficial, indolent ulcer." Wooley,[5] reporting on typical lesions of experimental tularemia in laboratory animals, describes the microscopic appearance of skin lesions (following scarification and puncture), as that of a diffuse, rapidly necrotic ulceration. Francis,[6] Goodpasture and House,[7] and other observers uniformly describe ulceration as the single type of primary tularemic lesion. A search of the literature revealed no previous reports of any similar variation from the classical type of primary lesion.

The dermal manifestations, too, were unusual, although it is known that tularemic skin rashes have a protean character. The skin involvement here resembled clinically the type sometimes seen in pyogenic septicemias, such as the painful, tender erythema overlying an early metastatic pyogenic osteomyelitis. In the opinion of Hitch and Smith,[3] tularemic eruptions are primarily a toxic, rather than a bacteremic or septicemic manifestation. They point out that many patients show the cutaneous eruptions when relatively afebrile. However, it is of interest to note that in this case the rash came on concomitantly with a secondary rise and spiking of temperature, and at this time the patient again appeared quite ill and was occasionally disoriented. This second clinically septic period was demonstrated to be concurrent with blood stream invasion by tularemic organisms. It would appear, therefore, that the eruption described here could more properly be termed "septic" rather than "toxic." The figures of Hitch and Smith give the average duration of tularemic rash as about 22 days. In this case, the rash lasted only eight days. It is possible that this short duration may have been due

to the administration of the sulfanilamide compounds; these were begun on the fifth day of the rash, at which time the skin lesions were quite florid.

The prognostic significance or seriousness of septicemia in tularemia is difficult to evaluate; clinical data upon this subject in the literature are meager. In a review of autopsied cases reported by Gundry and Warner,[8] only 4 of the 14 reviewed cases included results of premortem animal inoculation of patients' blood. In all of these four cases, the animal inoculations were positive for *B. tularense*. Postmortem animal inoculations were positive in all cases in which this procedure was carried out (7 out of 14). No conclusions are to be drawn from these figures; they are suggestive rather than conclusive. However, on the basis of the severe clinical relapse associated in this case with proved blood stream invasion by *B. tularense*, there would at least be reason to assume that tularemic septicemia, particularly when occurring late in the course of the disease, should be regarded with as much gravity as septicemia in the more common pyogenic infections.

SUMMARY

A wide variety of treatments has been used in severe or complicated cases of tularemia, ranging from phenol locally to salvarsan intravenously; this would seem to indicate that no really dependable therapeutic agent has yet been found. The therapeutic potentialities of sulfanilamide and its derivatives have yet to be fully explored. This case details an instance which suggests that sulfanilamide compounds may be bactericidal to blood-borne tularemic organisms. Laboratory studies and further clinical investigation are necessary to determine the efficacy of sulfanilamide and its derivatives in tularemia.

Tularemic septicemia may occur quite late in the course of the disease, and thereby present itself as a complication. An example of such an occurrence is detailed here.

The primary lesion of tularemia is not necessarily an ulcer. An unusual primary lesion, consisting of a cellulitis of two terminal phalanges of the hand, is described.

An unusual skin eruption, concurrent with the late septicemia, is described.

The use of sulfanilamide compounds, followed by rapid recovery, in an unusual, severe, and protracted case of tularemic septicemia, is reported.

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UNILATERAL RENAL TUBERCULOSIS ASSOCIATED WITH HYPERTENSION *

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BECAUSE Goldblatt [1] could, by removing the ischemic kidney in his experimental hypertensive dogs, cause a fall of blood pressure to normal, the possible clinical application of his results to cases of essential hypertension in man aroused considerable interest, particularly among internists and urologists. The following report deals with a case of unilateral renal tuberculosis with hypertension and the satisfactory result which has continued for 11 months after nephrectomy.

CASE REPORT

L. P., a married white male, aged 37 years, was admitted to the Latter-Day Saints Hospital on January 10, 1940, complaining of occipital headaches of extreme degree, fatigue, shortness of breath upon exertion, insomnia, extreme irritability and pounding of his heart.

Past History. At 13 years of age this patient had mumps accompanied by orchitis of the right testicle, resulting in its atrophy to one-third its normal size. At the age of 20 years he had what was diagnosed as typhoid fever. During this illness he had a leukocytosis ranging from 9,600 to 12,000, which is unusual for typhoid. He also developed a cough and an effusion in his left pleural cavity. This fluid did not reveal any organisms upon culture, and no tubercle bacilli were found in the sputum. The Widal reaction was positive, but there had been prior inoculations against typhoid fever.

He was married at 22 years and his wife had one child in the first year and none since. At 23 years of age (in 1925) he injured his left testicle. This resulted in a suppurating orchitis which drained spontaneously two months after the injury and continued for one year. In 1928 a diagnosis of tuberculous epididymitis on the left side was made, for which he refused operation.

Urinalysis at this time showed no albumin but an occasional red blood cell. His blood pressure was systolic 126 and diastolic 80 mm. Hg.

In 1930 the patient began to have attacks of hiccoughs which have since recurred intermittently. During the last five years he has had to get up once at night to void. In 1937 he began to have occasional headaches. His blood pressure was reported normal at that time but he does not know the exact readings.

Present Illness. During the latter part of 1938 some shortness of breath was noted upon exertion. In February 1939 he began to be nervous and irritable. The headaches became more frequent and severe. An examination in May 1939 revealed a systolic blood pressure of 180 mm. Hg. He weighed 189 pounds and was advised to lose weight.

In July 1939, while at an altitude of 11,000 feet, he became very short of breath, weak and faint. During that summer and fall insomnia developed, with increasing nervousness and irritability. He also complained of pains in his back in the region of his left kidney, and that his heart pounded very hard.

On January 10, 1940 he was admitted to the hospital, two days after a peculiar nervous attack which greatly alarmed his doctor and family. It consisted of severe headache associated with generalized numbness and twitching. The essential physical findings were: Weight 177 pounds, 12 pounds under his usual weight. Temperature 98.4° F.; pulse 82; blood pressure systolic 210, diastolic 150. He was extremely

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nervous, apprehensive and irritable; the reflexes were exaggerated but no abnormal ones were present. The heart showed accentuation of the second aortic sound with little or no enlargement either on percussion or on a seven foot roentgen-ray film. His blood vessels seemed neither tortuous nor obviously thickened. There was no palpable mass in the abdomen but there was some tenderness to hard percussion over his left kidney. There was a hard nodular mass in his left epididymis.

Laboratory findings: Blood, hemoglobin 87 per cent, red blood cells 5,150,000, white blood cells 10,750, the differential count being 81 per cent polymorphonuclear neutrophiles, 16 per cent lymphocytes, 2 per cent large mononuclears, and 1 per cent

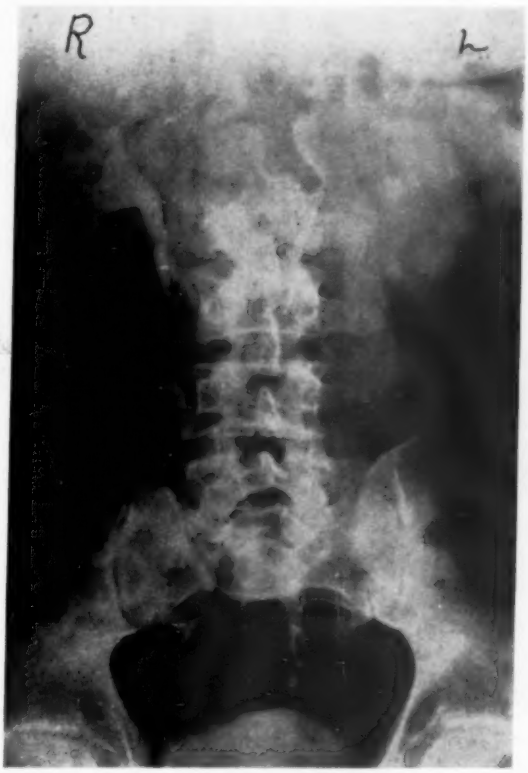

FIG. 1. Intravenous pyelogram showing normal right kidney and nonfunctioning left kidney.

eosinophiles. The urea nitrogen was 21.4 mg. per cent; the creatinine 1.08 mg. per cent. The Wassermann reaction was negative. Urine, specific gravity 1.012, alkaline, with a trace of albumin, and an occasional pus cell. The urine concentration test ranged from 1.009 to 1.022. The phenolsulfonphthalein output was normal. Spinal puncture revealed normal pressure, normal jugular response and normal fluid. Intravenous pyelograms on two occasions showed a normal right kidney and ureter, but no shadow at all on the left side. Cystoscopy showed a normal ureter and kidney with normal function on the right side, but merely a small dimple at the site of the left ureteral orifice from which no urine or dye appeared.

The fundi showed a slight tortuosity of the vessels with mild arterio-venous compression; no hemorrhages, exudates, or edema of the disc.

He had a labile type of hypertension and under sedation with sodium amytal his blood pressure dropped as low as systolic 150, diastolic 100. The headaches were relieved with the drop in pressure.

On the fifteenth day of his hospital stay Dr. Ralph Richards removed the left kidney. The kidney was less than one-half its normal size, weighing 73 gm. The pelvis was distended with a thick caseous material which also filled the ureter. There was a considerable amount of fairly healthy looking kidney cortex to which the capsule was only slightly adherent.

Microscopically it showed hyalinization of all the glomeruli and marked increase in interstitial tissue which constricted the tubules. There were giant cells in some areas. The vessels of the pedicle and all the small arterioles showed marked intimal proliferation with narrowing of the lumen. The pathological diagnosis was tuberculosis of the kidney with advanced caseation, and arteriosclerosis.

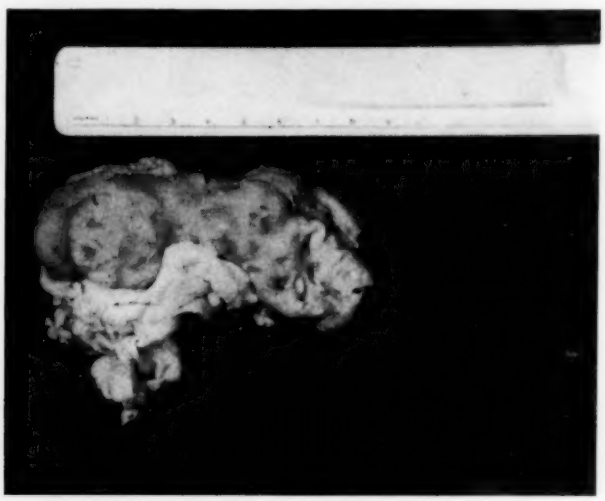

FIG. 2. Gross specimen of left kidney weighing 73 gm.

At the beginning of the operation the pressure was systolic 230, diastolic 140, and the pulse 92. After the kidney pedicle was clamped, the pressure began to fall. One hour after completion of the operation it was systolic 102, diastolic 80. It dropped as low as systolic 80 and 60 diastolic after operation. A transfusion of 500 c.c. of blood was given, and the blood pressure rose to systolic 120, diastolic 80. During the next 15 days it ranged from systolic 154 to 176 and diastolic 88 to 108, and seemed to depend upon the amount of pain present.

Fifteen days after the nephrectomy his left epididymis was removed. At the time of discharge from the hospital, the blood pressure was systolic 130, diastolic 74, and the patient was symptom free.

During the next 11 months the pressure has ranged from systolic 118 to 128 and diastolic 78 to 86. He is now back at work and apparently cured of all his complaints except some backache.

Among the cases reported since Goldblatt's communication are Butler's [2] two cases in children with hypertension and unilateral pyelonephritis in whom nephrectomy was followed by return to normal blood pressure. One case, in a child of 10 years, was reported by Barney and Suby,[3] and three were reported by

Crabtree.[4] Leadbetter and Burland [5] reported the case of a negro boy, age five and one half years, who was known to have had hypertension for three years, with complete relief after removal of an ectopic kidney in which the main artery was partially occluded. Boyd and Lewis [6] reported similar results after removal of a kidney containing multiple infarcts. Barker and Walters [7] of the Mayo Clinic reported five cases of unilateral pyelonephritis associated with hypertension in patients ranging in age from 7 to 52 years. After removal of the kidney in all these cases the blood pressure returned to normal. Their report covered a postoperative period of from 6 to 29 months. The mean blood pressure before operation varied from systolic 178 to 210 and diastolic 118 to 166. All kidneys removed weighed 75 gm. or less (less than half the normal size) and all the kidneys showed a considerable thickening of the arterial walls in the areas of

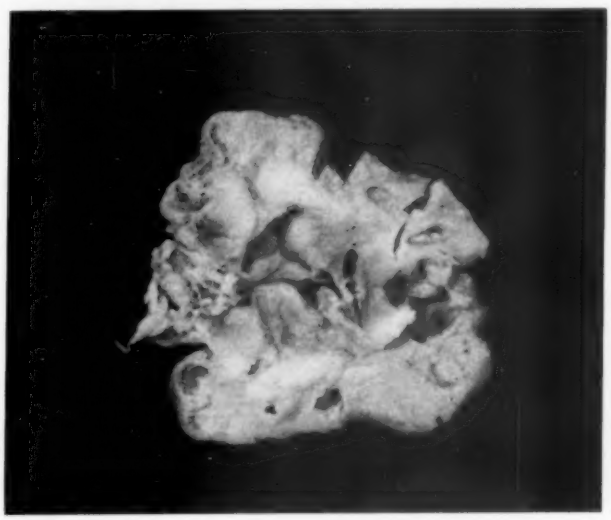

FIG. 3. Cut specimen of same kidney.

definite renal sclerosis. None of the cases had evidence of advanced generalized arterial damage.

A very instructive case was reported by Fitz.[8] A man 40 years of age with a history of pain in the right side of his abdomen for four years, for which appendectomy had given no relief, developed headaches, persistent hypertension, acute hemorrhagic nephritis following acute tonsillitis, and later hemorrhagic retinitis. He had had a bilateral sympathectomy with no relief in 1937. One year later, because the right kidney seemed smaller in the urogram than when examined the year before, and in spite of an apparent normal kidney function, his right kidney was removed. It weighed only 30 gm. His pressure returned to normal, all his symptoms disappeared, and he has remained well since.

Undoubtedly the cases in which the so-called Goldblatt kidney is the cause of hypertension in man are comparatively rare. Up to date, probably not more than 20 have been reported. So far as I have reviewed the literature, this is the only case yet reported of relief of hypertension associated with removal of a tuberculous kidney.

The varied pathological conditions found in the kidneys removed on account of hypertension, as listed in the accompanying bibliography, and the results following nephrectomy in carefully studied and selected cases, would seem to be sufficient justification for special urological study in most all cases of so-called essential hypertension, the majority of which will reveal no unilateral kidney disease.

However, the drop in blood pressure and the relief of symptoms which may follow the removal of a unilateral hydronephrotic or pyonephrotic kidney associated with hypertension, is a result to be sought.

We have studied our hypertensives more carefully during the past year and have discovered two patients who presented no symptoms referable to their hydronephrotic kidneys.

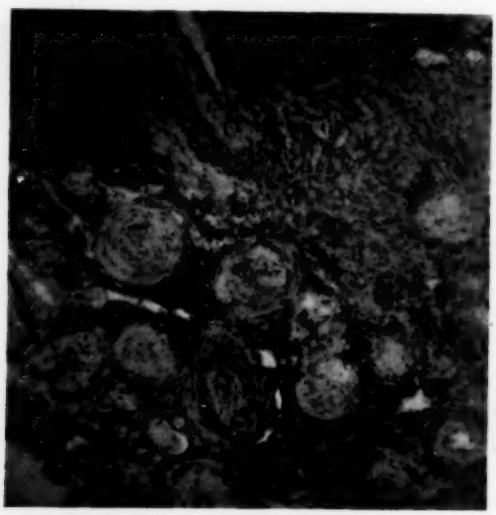

FIG. 4. Microphotograph of kidney showing the marked blood vessel changes.

It is too soon to venture an opinion as to the length of time one might expect this relief of the hypertension to continue following unilateral nephrectomy in these cases. Many investigators think it depends upon the condition of the remaining kidney.

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EDITORIAL

THE PATHWAY OF INFECTION IN POLIOMYELITIS

THE problem of the pathogenesis of poliomyelitis—its portal of entry, the manner of the distribution of the virus in the body tissues and the route by which it is disseminated—has not yet been satisfactorily solved, in spite of much intensive investigation.

The study of the disease is beset with many practical difficulties. One of the greatest of these is the fact that the monkey is the only animal susceptible to the filtrable virus which causes the disease, and successful inoculation of these animals is the only method of demonstrating its presence. Even monkeys appear to differ in susceptibility, and individual animals may escape infection or present subclinical or abortive attacks without the typical paralysis. Relatively large doses appear to be required to infect the monkey, as compared with many other filtrable viruses, and this animal can not be regarded as a sensitive indicator of the virus. It is, therefore, necessary to use several animals in important experiments.

Although by special methods mice can be infected with certain passage strains, they are not susceptible to inoculations of human material, and failure to produce an encephalitis by intracerebral inoculation of virus into mice and other common laboratory animals is one criterion for the identification of the virus.

Epidemiological and clinical studies of human cases have shown great individual variation in susceptibility. Evidently many are naturally refractory or become so as the result of a subclinical infection. Even among those clinically ill it is probable that there are from four to six abortive cases to each one showing the typical paralytic lesions. There is as yet no practicable means of identifying such cases positively, and the diagnosis is rarely even suspected except during an epidemic. Although occasional instances have been reported in which direct contact infection has occurred, this is relatively rare. In most cases infection must be acquired from abortive cases or carriers. Such observations, however, have shed little light on the problems under discussion.

The virus of poliomyelitis has a special predilection for the nervous system, in which the characteristic lesions are found. It is generally believed that the virus reaches the nervous system by centripetal passage through the nerve trunks. Nonmedullated fibers appear to be especially vulnerable to attack. The possibility of transmission by lymph and blood stream has also been claimed, particularly by Kling and Levaditi, but their experiments are open to criticism.

After reaching the central nervous system the virus becomes widely disseminated, presumably by direct extension, throughout the motor areas in the cortex, medulla and entire spinal cord. This has been shown by inoculation of tissue from these regions into monkeys, and also by the occurrence here of the typical histological lesions, consisting of necrosis and disappearance of motor cells, and round cell infiltrations about the vessels and in the gray matter. It has also been shown that in monkeys there is a centrifugal spread of virus to the periphery along the nerve trunks, such as occurs in rabies.

Flexner has long maintained that the nasopharynx constitutes the portal of entry, and probably also of exit of the virus. This view is based in part on the fact that the virus has been demonstrated repeatedly (although not regularly) in washings from the nasopharynx, and in extracts of the mucosa of that region in human cases. Monkeys can easily be infected by intranasal inoculations of virus, and the infecting dose is smaller than when given by injection in other regions. The virus is believed to enter through the olfactory mucous membrane and to reach the brain by passage through the olfactory tracts. This view is supported by the presence of typical histological lesions in the olfactory bulbs of monkeys so inoculated, although according to Sabin and Olitsky they are not present in animals infected by other routes. It has been generally assumed that this is also the mode of infection in man, and that the virus is disseminated in the nasal secretions, by droplet infection.

Other investigators, however, have held that the portal of entry is to be found in the gastrointestinal tract. This view has recently received support from Levaditi and Kling [1] on the basis of feeding experiments. By introducing virus through a stomach tube as well as by feeding materials contaminated with virus, they succeeded in infecting several animals. They also obtained infection by injecting virus, by needle, directly into the lumen of the ileum. In two cases they found virus in the mesenteric glands, and they think it may reach the brain through the circulation.

Flexner [2] and his associates, however, repeated these experiments with essentially negative results. The occasional successful case they attributed to contamination of the nasal mucosa with the virus, or to introduction of virus into the tissues of the intestinal wall by the needle.

There is now conclusive proof that the virus occurs in the feces, sometimes in considerable concentration, and that it may remain viable there for substantial periods of time. Thus, Paul, Trask and their associates [3] demonstrated virus in 10 of 56 specimens examined, obtained from cases of the

[1] Levaditi, C., Kling, C., and Hornus, G.: Transmission expérimentale de la poliomyélite par la voie digestive, Compt. rend. Soc. de biol., 1933, cxii, 43–45.

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disease in several different epidemics. Positive results were obtained with two specimens which had been in the mail (from England) for two weeks in summer weather before they were examined. They[4] were also able to demonstrate virus in several instances in sewage taken from mains in the vicinity of isolation hospitals during epidemics of the disease. In one specimen the virus had survived in sewage which had flowed for at least one sixteenth of a mile. If the virus were uniformly distributed throughout the sewage there would have been 18,000 infective doses per minute discharged at that point.

Thus far, however, there is no direct proof that infection is conveyed in this manner. The virus might be swallowed after being eliminated in the nasopharynx, and its presence in the feces merely an incidental phenomenon.

Recently Sabin and Ward[5] have tried to get additional evidence bearing on this problem by a study of the distribution of the virus in human tissues. They point out that although there are many reports of the isolation of virus from various human tissues, there have been no comprehensive studies of many tissues from the same individual. Accordingly they inoculated monkeys with 22 different tissues from each of nine fatal cases of human poliomyelitis. In two cases they failed to demonstrate any virus, but in the other seven cases they recovered it from two or more sites.

In general their results do not support the view that the virus enters through the olfactory pathway. Although usually found in the motor areas of the brain and cord, in no case was it found in the olfactory bulbs, and these did not show the histological lesions characteristic of the bulbs of monkeys infected by the nasal route. In no case was virus demonstrated in the nasal mucosa, although it was found in the mucosa of the pharynx in four cases. It was found in three cases in the washed wall of the ileum, although not demonstrated in the contents of the ileum in two of them. It was found in the contents of the ileum in two cases, and in those of the descending colon in all six cases in which material was available for examination.

The failure to demonstrate virus in the salivary glands, suprarenal glands, lymph nodes or sympathetic ganglia (with one exception) led them also to question the theory of a centrifugal distribution of virus from the central nervous system through the nerve trunks. They concluded that their findings point to the gastrointestinal tract as the portal of entry and site of primary localization of the virus.

The evidence presented by these investigators is manifestly indirect, but it raises serious doubt as to whether the virus entered through the olfactory

[4] Paul, J. R., Trask, J. D., and Gard, S.: II. Poliomyelitic virus in urban sewage, Jr. Exper. Med., 1940, lxxi, 765–778.

[5] Sabin, A. B., and Ward, R.: The natural history of human poliomyelitis. I. Distribution of virus in nervous and non-nervous tissues, Jr. Exper. Med., 1941, lxxiii, 771–794.

pathway in these cases. It is impossible to reconcile these findings with the work and views of Flexner except by assuming either that these cases were all highly exceptional, or that man differs radically from the monkey in his response to the virus. Further investigations are obviously needed to decide the question. Until this is accomplished, the frequent presence of the virus in the feces is a fact which can not safely be disregarded.

P. W. C.

REVIEWS

Arthritis and Allied Conditions. By BERNARD I. COMROE, A.B., M.D., F.A.C.P. Second Edition. 878 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. 1941. Price, $9.00.

This book is really the complete story of arthritis as known today. It begins with the occurrence of the disease in the prehistoric period of man and beast and ends with the latest information on the sulfonamides. The 50 chapters and 2644 bibliographic references give ample evidence of the wide extent of the author's review of the literature and his tremendous amount of work. The illustrations are excellent and indeed speak for themselves. In addition to the chapters on etiology and pathology and general therapy a large portion of the book is devoted to the special methods of treatment, such as fever therapy, massage and kinds of shoes to be worn. The author's therapeutic recommendations show conservatism and caution, for example, while his statistics on gold therapy are quite encouraging, yet every patient is asked to sign a statement, witnessed by two additional persons, "assuming the responsibility for complications which might arise from this form of therapy." In the experience of this reviewer such a procedure is urgently recommended.

The related conditions cover a wide field such as painful feet, backache, internal derangement of the knee joints, tumors of joints and tendon sheaths and the sulfonamides. The text is well written, the style is easy to read in spite of the many assembled details. An attractive feature for the busy general practitioner is the inclusion of summaries presented in box form outlines, enabling him to obtain quickly most of the information he requires.

The book is based on the author's personal experiences but it contains a comprehensive review of the literature. It can be highly recommended as an excellent and up to date reference book which will have an especial appeal to the internist and orthopedist.

L. A. M. K.

Modern Diabetic Care. By HERBERT POLLACK, A.B., Ph.D., M.D. 216 pages; 21 × 14 cm. Harcourt, Brace and Co., New York. 1940. Price, $2.00.

This is a complete manual designed for the diabetic patient. Throughout the book, of about 200 pages, technical language has been avoided but where used has been well explained in lay terms. The diabetic diet is discussed in a simple and complete manner. "The highly important matter of feeding the diabetic is not one that requires careful minute specialization. Rather, it is only a problem of making slight alterations and simple adjustments in a well balanced, normal diet." Probably if this statement were really understood and practiced, diabetics as a group would be receiving far better treatment today.

The chapter on protamine zinc insulin is most valuable to both patient and physician. The rather brief discussion of the problems: Shall Diabetics Marry? Are Diabetics Safe Automobile Drivers? For What Trade May Young Diabetics Be Trained? are most valuable. There are the sections dealing with food equivalents and substitutions, recipes, and food combinations usually found in books of this type. The index is complete and workable.

There are already many diabetic manuals in print but the reviewer feels that this small volume occupies an unusual position. Throughout the many interesting chapters the author has kept in mind that the patient is just a busy layman, not trained in medicine, but interested in finding out briefly but thoroughly how to care for his diabetes. The book is most heartily recommended.

H. P.

The Endocrine Function of Iodine. By WILLIAM THOMAS SALTER, Assistant Professor of Medicine, Harvard Medical School. 351 pages; 24 × 16 cm. Harvard University Press, Cambridge, Massachusetts. 1940. Price, $3.50.

This volume is one of the Harvard University Monographs in Medicine and Public Health. The title gives only a hint of the complete review of the subject presented by the author. A survey of some headings in the table of contents may suggest the comprehensive character of the work.

The introductory chapter discusses briefly iodine balance and endocrine balance. Other chapters take up iodine stores in body tissues, iodine compounds of biological importance, circulating iodine in air, lymph, cerebrospinal fluid, milk, sweat, saliva and blood. In the chapter on circulating iodine, the discussion of blood iodine is most complete and detailed.

Later chapters are concerned with thyroid activity, endocrine balance, iodine and the "pituitary-ovarian axis," neurological influence of the thyroid hormone, and studies with radioactive iodine. The final chapter is probably the most interesting to the practicing physician, and introduces some clinical problems. Cases studied at the Boston City Hospital are reported, and the value of blood iodine determinations in the differential diagnosis of thyroid disease is discussed.

The book closes with a 20 page appendix for laboratory workers, describing methods for the determination of the blood iodine content, and separation of protein and non-protein fractions.

T. N. C.

Landmarks in Medicine. Laity Lectures of the New York Academy of Medicine. Introduction by JAMES ALEXANDER MILLER, M.D. 347 pages; 20 × 13.5 cm. D. Appleton-Century Company, New York. 1939. Price, $2.00.

The New York Academy of Medicine, through its annual series of "Laity Lectures," has done much to stimulate interest in medical history and thus foster a better mutual understanding between the medical profession and the laity. "Landmarks in Medicine" is the third publication in this series. In the introduction it is stated, "The New York Academy of Medicine has long recognized as an obligation the interpretation of the progress of medical knowledge to the public."

The eminent contributors to this volume and their subjects are as follows: "From Barber-Surgeons to Surgeons" by Francis R. Packard, M.D.; "The Meaning of Medical Research" by Alfred E. Cohn, M.D.; "Dr. Watson and Mr. Sherlock Holmes" by Harrison Stanford Martland, M.D.; "Medicine in the Middle Ages" by James J. Walsh, M.D.; "The Search for Longevity" by Raymond Pearl, M.D.; "Medicine and the Progress of Civilization," by Reginald Burbank, M.D.; and "X-Ray Within the Memory of Man," by Lewis Gregory Cole, M.D.

While this little book may be read with real interest by the layman for whom it was intended, it will also be warmly appreciated by any member of the medical profession.

J. E. S.

The Early Diagnosis of the Acute Abdomen. By ZACHARY COPE, B.A., M.D., M.S. Lond., F.R.C.S. Eng. 257 pages; 22.5 × 14.5 cm. Oxford University Press, New York. 1940. Price, $3.75.

An excellent compendium or roll-call of the conditions which are commonly responsible for the acute abdomen, stressing the history, methods of examination and differential points for early diagnosis.

This illustrated book written in large print, limited to 244 pages, should prove of particular value, first to students, in giving them an organized and concise picture of

such a vast subject, and second to practitioners, in giving a review of diseases so consistently and commonly responsible for abdominal distress.

The author stresses the value of history taking, examination, anatomy and physiology in the interpretation of symptoms in making a diagnosis. Laboratory work, though mentioned, is not accentuated, which may be considered justifiable since so many surgical patients are first seen in homes where laboratory facilities are nil and the doctor must rely on other criteria in reaching a diagnosis.

Common surgical conditions are reiterated. Rarer diseases are mentioned in differential diagnostic tables, though no mention was made of nonspecific terminal ileitis, mesenteric adenitis, Meckel's diverticulitis, or rupture of the corpus luteum, conditions which in late years have gained some notice.

As evidenced by the many editions of this publication, a summary of so large a subject is still well received.

H. C. H.

COLLEGE NEWS NOTES

Gifts to the College Library

Acknowledgment is made of the receipt of the following reprints by members of the College:

Dr. Robert H. Bayley, F.A.C.P., New Orleans, La.—8 reprints;
Dr. Victor W. Bergstrom, F.A.C.P., Binghamton, N. Y.—1 reprint;
Dr. Edward G. Billings, F.A.C.P., Denver, Colo.—*2* reprints;
Dr. Edward W. Bixby, F.A.C.P., Wilkes-Barre, Pa.—1 reprint;
Dr. Hildahl I. Burtness, F.A.C.P., Santa Barbara, Calif.—*2* reprints;
Dr. Verne S. Caviness, F.A.C.P., Raleigh, N. C.—*2* reprints;
Dr. Richard E. Ching, F.A.C.P., Memphis, Tenn.—1 reprint;
Dr. William P. Garver (Associate), Cleveland, Onio—*2* reprints;
Dr. Edward S. King, F.A.C.P., Winston-Salem, N. C.—*2* reprints;
Dr. Phillip T. Knies, F.A.C.P., Columbus, Ohio—6 reprints;
Dr. Charles J. Koerth (Associate), San Antonio, Tex.—*2* reprints;
Dr. Charles A. LaMont, F.A.C.P., Canton, Ohio—*2* reprints;
Dr. Rudolf Leiser, F.A.C.P., Eloise, Mich.—1 reprint;
Dr. William H. Ordway, F.A.C.P., Mount McGregor, N. Y.—*2* reprints;
Dr. Dale P. Osborn, F.A.C.P., Cincinnati, Ohio—1 reprint;
Capt. John R. Poppen, F.A.C.P., (MC), U. S. Navy—1 reprint;
Dr. Ellen C. Potter, F.A.C.P., Trenton, N. J.—1 reprint;
Dr. Harry Plummer Ross (Associate), Richmond, Ind.—1 reprint;
Dr. Ernest G. Scott, F.A.C.P., Lynchburg, Va.—1 reprint;
Dr. Bernard Seligman (Associate), Brooklyn, N. Y.—*2* reprints;
Dr. Hugh Smith, F.A.C.P., Greenville, S. C.—1 reprint;
Dr. Edward R. Snader, Jr., F.A.C.P., Philadelphia, Pa.—18 reprints;
Dr. Harry P. Thomas (Associate), Rusk, Tex.—*2* reprints;
Dr. Henry J. Tumen (Associate), Philadelphia, Pa.—1 reprint;
Dr. Edward L. Turner, F.A.C.P., Nashville, Tenn.—4 reprints;
Dr. F. Howard Westcott, F.A.C.P., New York, N. Y.—1 reprint;
Dr. Arthur T. Wyatt, F.A.C.P., Lillington, N. C.—1 reprint.

A.C.P. Becomes Member, Division of Medical Sciences of the National Research Council

The American College of Physicians has been appointed by the unanimous action of the Executive Board of the National Research Council a member society in the Division of Medical Sciences of that body. Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia, has been appointed the College representative in the Division. Dr. Pepper is also Chairman of the Committee on Medicine of the Division of Medical Sciences of the Council.

The National Research Council was established in 1916 by the National Academy of Sciences under its congressional charter and supported by the coöperation of national scientific and technical societies of the United States. The Council is a representative organization of the scientific men of America. Its members include not only scientific and technical men, but also business men interested in engineering and industry. The membership of the Council is composed largely of appointed representatives of the scientific and technical societies and includes representatives also of certain other research organizations, representatives of Government scien-

tific bureaus, and a limited number of members at large. The Council actually was organized at the request of President Woodrow Wilson as a measure of national preparedness. The work accomplished by the Council in organizing research and in securing coöperation of military and civilian agencies in the solution of military problems demonstrates its capacity for larger service. The Council is carried on by a small group of officers and an Executive Board, with an Administrative Committee which acts for the Board between its annual meetings. The Council is composed of nine major divisions, arranged in two groups. One group comprises seven divisions of science and technology, the other group comprises two divisions of general relations, representing foreign relations and educational relations. The Division of Medical Sciences is one of the seven divisions of science and technology, and Dr. Lewis H. Weed, Professor of Anatomy and Director of the School of Medicine of Johns Hopkins University, Baltimore, is the Chairman. The Division has more than a score of committees and sub-committees, and it coöperates with other Divisions of the Council in connecting with the activities of some of their committees. A large proportion of its committee chairmen and members are Fellows of the American College of Physicians.

The newly-organized American Diabetes Association held its First Annual Session at Cleveland, June 1, 1941. Its initial officers were:

Elliott P. Joslin, M.D., F.A.C.P., Boston, Honorary President
Cecil Striker, M.D., F.A.C.P., Cincinnati, President
Herman O. Mosenthal, M.D., F.A.C.P., New York City, First Vice-President
Joseph T. Beardwood, Jr., M.D., F.A.C.P., Philadelphia, Second Vice-President
Samuel S. Altshuler, M.D., F.A.C.P., Detroit, Secretary
William Muhlberg, M.D., Cincinnati, Treasurer

Over 350 physicians attended the meeting, and it has been decided that the next meeting will be held on the day preceding the opening of the American Medical Association meeting at Atlantic City, June, 1942.

Current officers include:

Herman O. Mosenthal, M.D., F.A.C.P., President
Joseph T. Beardwood, Jr., M.D., F.A.C.P., First Vice-President
Joseph Barach, M.D., F.A.C.P., Pittsburgh, Second Vice-President
Cecil Striker, M.D., F.A.C.P., Secretary
William Muhlberg, M.D., Treasurer

Among members of its Board of Trustees are:

Dr. James E. Paullin, F.A.C.P., Atlanta; Dr. W. D. Sansum, F.A.C.P., Santa Barbara; Dr. Edward S. Dillon, F.A.C.P., Philadelphia; Dr. James Ralph Scott, F.A.C.P., New York City; Dr. H. Clare Shepardson, F.A.C.P., San Francisco; Dr. L. H. Newburgh, F.A.C.P., Ann Arbor; Dr. Russell M. Wilder, F.A.C.P., Rochester, Minn.; Dr. Seale Harris, F.A.C.P., Birmingham; Dr. Henry John, F.A.C.P., Cleveland; Dr. Edward H. Mason, F.A.C.P., Montreal; Dr. Howard F. Root, F.A.C.P., Boston.

The Association is engaged in appointing committees, to study the problem of the publication of a journal, to work with the American Dietetic Association on the question of foods and diets, to coöperate with the Federal Food and Drug Administration on fraudulent diabetic cures; to study the problem of assisting in the foundation of local diabetes associations.

Dr. Clifford W. Mack, F.A.C.P., Livermore, Calif., was recently elected an Administrative Member at large of the California Physicians Service by its Board of Trustees.

Dr. William A. Groat, F.A.C.P., Syracuse, N. Y., has been elected Chairman of the Board of Trustees of the Medical Society of the State of New York for the 1941–42 term.

Dr. Jacob Casson Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, recently received the Officer's Cross of the Order of the Southern Cross of Brazil. This decoration was conferred by President Vargas of Brazil with the following citation: "For eminency in preventive medicine and public health."

On July 10, 1941, the 11th Councilor District of the Medical Society of the State of Pennsylvania held its annual meeting in Johnstown. "The Management of Allergic Conditions of the Respiratory Tract" and "Silicosis" were among the topics discussed. Dr. Francis F. Borzell, Philadelphia, President of the Medical Society of the State of Pennsylvania spoke on "Medical Preparedness." Dr. Laurrie D. Sargent, F.A.C.P., Washington, Trustee and Councilor, presided.

Dr. Alexander H. Stewart, F.A.C.P., Harrisburg, Pa., was recently appointed Acting Director of the Pennsylvania State Department of Health, succeeding Dr. John Shaw, who died suddenly June 24, 1941.

Dr. Allen H. Bunce, F.A.C.P., Atlanta, has been installed as President of the Medical Association of Georgia.

Dr. Frank N. Wilson, F.A.C.P., Ann Arbor, Mich., was recently elected an honorary member of the Cardiac Society of Great Britain and Ireland.

Dr. Francis D. Murphy, F.A.C.P., Milwaukee, Wis., spoke on "Clinical Application of the Sulfonamide Group of Drugs" at a meeting of the Upper Peninsula Medical Association in Ironwood, Mich., July 17–18, 1941.

Dr. Thomas K. Lewis, F.A.C.P., Camden, was installed as President of the Medical Society of New Jersey at its annual meeting in Atlantic City, May 20–22, 1941. Dr. Ralph K. Hollinshed, F.A.C.P., Westville, was elected a Vice-President of the Society.

At the recent annual meeting of the State Medical Association of Texas held in Fort Worth, Dr. Neil D. Buie, F.A.C.P., Marlin, was installed as President. Dr.

Caleb O. Terrell, F.A.C.P., Fort Worth, was elected one of the Vice-Presidents of the Association.

Dr. Maurice C. Pincoffs, F.A.C.P., Baltimore, Md., was one of the lecturers at the 25th Anniversary Course of Lectures and Clinics presented by the University of Washington, July 14–18, 1941.

Dr. Bruce H. Douglas, F.A.C.P., Detroit, Mich., was elected President of the National Tuberculosis Association at its recent annual meeting in San Antonio, Tex., and Dr. J. Burns Amberson, Jr., F.A.C.P., New York, N. Y., was named President-Elect. Dr. Henry F. Carman, F.A.C.P., Dallas, Tex., was elected a Vice-President of the Association.

Dr. David C. Wilson, F.A.C.P., Charlottesville, Va., was elected one of the Vice-Presidents of the American branch of the International League Against Epilepsy at its annual meeting in Richmond, Va., May 5, 1941.

Dr. Arthur M. Master, F.A.C.P., and Dr. Frederick R. Bailey, F.A.C.P., have been promoted to Assistant Clinical Professors of Medicine at Columbia University College of Physicians and Surgeons, New York, N. Y.

Among the speakers at a joint meeting of the 6th and 8th Councilor Districts of the State Medical Society of Wisconsin held in Appleton, May 27, 1941, were:

Dr. William S. Middleton, F.A.C.P., Madison, Wis.—"Bronchiogenic Carcinoma";

Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn.—"Puzzling Types of Indigestion" and "Food Allergy."

Dr. John A. Toomey, F.A.C.P., Cleveland, Ohio, spoke on "Pathogenesis of Poliomyelitis" at the annual meeting of the Iowa and Illinois Central District Medical Association, June 26, 1941, in Davenport, Iowa.

Dr. John T. Murphy, F.A.C.P., Toledo, Ohio, delivered the 1941 Hickey Memorial Lecture at a joint meeting of the Wayne County Medical Society and the Detroit Roentgen Ray and Radium Society, April 7, 1941. Dr. Murphy spoke on "The Use of X-Ray in the Treatment of Carcinoma of the Skin."

Dr. David B. Jewett, F.A.C.P., Rochester, N. Y., was awarded the Albert D. Kaiser Medal "for distinguished service to the medical profession" at the annual meeting of the Rochester Academy of Medicine, May 6, 1941. Dr. Jewett received this award for his efforts in building up the Academy's library.

On May 26, 1941, Dr. Graham Asher, F.A.C.P., Kansas City, Mo., addressed the Tulsa (Okla.) County Medical Society on "Chemical, Nutritional and Clinical Factors Influencing the Administration of Digitalis."

Dr. John S. Hibben (Associate), Pasadena, Calif., spoke on "Clinical Evaluation of Various Heart Energies" at the 9th Annual Seminar of the Western Section of the American Congress of Physical Therapy held in Los Angeles, Calif., June 22, 1941.

Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, has been elected Vice President of the American Society of Clinical Pathologists.

Dr. Benjamin Goldberg, F.A.C.P., Chicago, Ill., was installed as President of the American College of Chest Physicians at its annual meeting in Cleveland, Ohio, May 31–June 2, 1941. Dr. J. Winthrop Peabody, F.A.C. P., Washington, D. C., was named President-Elect of this society and Dr. Jay Arthur Myers, F.A.C.P., Minneapolis, Minn., a Vice-President.

Dr. John T. Murphy, F.A.C.P., Toledo, Ohio, was one of the speakers at the 7th Midsummer Radiologic Conference of the Denver Radiological Club, which was held July 31–August 2, 1941. Dr. Murphy spoke on "Carcinoma of the Skin."

Dr. Roy L. Leak, F.A.C.P., Middletown, has been chosen President-Elect of the Connecticut State Medical Society.

Dr. Henry N. Tihen, F.A.C.P., Wichita, was named President-Elect of the Kansas Medical Society at its annual meeting in Topeka in May. Dr. John M. Porter (Associate), Concordia, was reëlected Secretary of the Society.

Dr. Herbert Z. Giffin, F.A.C.P., Rochester, has been elected President of the Minnesota State Medical Association. Dr. Benjamin B. Souster, F.A.C.P., St. Paul, was reëlected Secretary of the Association.

On May 29, 1941, Dr. Joseph H. Barach, F.A.C.P., Pittsburgh, Pa., addressed the Glens Falls (N. Y.) Academy of Medicine on "Present Day Treatment of Diabetes and Its Complications," and spoke on "Inheritance and Tumors" at the Albany Medical College, Albany, N. Y.

The Board of Estimate and City Council of the City of New York have authorized the establishment, under the New York City Department of Health, of the Public Health Research Institute of New York, Inc. This Institute is to be used exclusively for scientific research "essential for the protection and the improvement of the health, safety and welfare of the people of New York City." This Institute will be directed by a lay board to supervise the business management and a research council to retain

the necessary scientific personnel. Dr. George Baehr, F.A.C.P., New York, N. Y., was named a member of the research council.

Among the speakers at the recent meeting of the Multnomah County Medical Society, Portland, Ore., May 7, 1941, were:

Dr. Donald E. Forster (Associate), Portland—"Vitamin B Complex";
Dr. Merl L. Margason, F.A.C.P., Portland—"Migraine."

On June 11, 1941, Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio, addressed the Washington County Medical Society, Washington, Pa., on gout.

Dr. Roy R. Snowden, F.A.C.P., Pittsburgh, College Governor for Western Pennsylvania, discussed "Newer Concept of Hypertension" at the meeting of the Cambria County Medical Society at Johnstown, Pa., June 12, 1941.

The Rhode Island Medical Society held its annual meeting at Newport, June 1, 1941. Among the speakers were:

Dr. Willard O. Thompson, F.A.C.P., Chicago, Ill.—"Sex Hormones: Clinical Application";
Dr. B. Earl Clarke, F.A.C.P., Providence, R. I.—"Intercapillary Glomerular Sclerosis or Diabetes-Nephrosis Syndrome."
Dr. Charles F. Gormly, F.A.C.P., Providence, was elected one of the Vice Presidents of the Society at this meeting.

The Wisconsin Anti-Tuberculosis Association held one-day institutes on "Diseases of the Chest" in ten towns between July 21 and August 1, 1941. The programs consisted of symposia on roentgen rays, lectures on significance of primary tuberculosis, differential diagnoses of diseases of the chest and pulmonary abscesses, and round table discussions. Among the lectures at these institutes were: Dr. Harold M. Coon, F.A.C.P., Statesan, Dr. Oscar Lotz, F.A.C.P., Milwaukee, and Dr. George C. Owen (Associate), Oshkosh.

Dr. Theodore G. Klumpp, F.A.C.P., Chicago, Ill., spoke on "The Philosophy of the Administration of the Drug Sections of the Food, Drug and Cosmetic Act" at the 45th Annual Conference of the Association of Food and Drug Officials of the United States, held at St. Paul, Minn., June 9–13, 1941.

The Association for the Study of Internal Secretions held its annual meeting in Atlantic City, N. J., May 2–3, 1941, under the Presidency of Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis. Dr. Edward H. Rynearson, F.A.C.P., Rochester, Minn., spoke on "Desoxycorticosterone in Prevention of Surgical Shock."

Dr. Henry H. Turner, F.A.C.P., Oklahoma City, Okla., was elected Secretary of the Association at this meeting.

At the annual meeting of the American Association for the Study of Allergy in Cleveland, Ohio, June 2–3, 1941, Dr. Milton B. Cohen, F.A.C.P., Cleveland, Ohio, was installed as President. Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill., was named President-Elect, and Dr. Oscar Swineford, Jr., F.A.C.P., Charlottesville, Va., Vice-President. Dr. James Harvey Black, F.A.C.P., Dallas, Tex., was reëlected Secretary.

At the recent annual meeting of the American Association of the History of Medicine held in Atlantic City, N. J., Dr. Jabez H. Elliott, F.A.C.P., Toronto, Ont., was installed as President, and Dr. Logan Clendening, F.A.C.P., Kansas City, Mo., was named President-Elect.

Dr. Edward A. Strecker, F.A.C.P., Philadelphia, Pa., has been elected First Vice-President of the American Neurological Association.

An honorary degree of Doctor of Laws was awarded to Dr. Rock Sleyster, F.A.C.P., June 11, 1941, by Marquette University.

Additional Hospitals Approved for Residencies

Dr. Hugh J. Morgan, Nashville, Tennessee, and Dr. O. H. Perry Pepper, Philadelphia, Pa., are the two appointees by the American College of Physicians on the Conference Committee on Graduate Training in Medicine, the Committee being composed also of representatives from the American Board of Internal Medicine and the Council on Medical Education and Hospitals of the American Medical Association. The Conference Committee at a recent meeting in Cleveland recommended the approval of the following hospitals for residencies in medicine, and this recommendation was accepted by the Council on June 3:

St. Francis Hospital, Evanston, Illinois
Massachusetts Memorial Hospitals, Boston
Butterworth Hospital, Grand Rapids, Mich.
St. Joseph Hospital, Kansas City, Missouri
St. Mary's Hospital, Kansas City, Missouri
New Rochelle Hospital, New Rochelle, N. Y.
St. Francis Hospital, Columbus, Ohio
St. Vincent's Hospital, Toledo, Ohio
Mount Sinai Hospital, Philadelphia
Presbyterian Hospital, Philadelphia
Chesapeake and Ohio Hospital, Clifton Forge, Va.

The American Board of Internal Medicine
Announcement of Examinations

The American Board of Internal Medicine will conduct written examinations October 20, 1941, and oral examinations just in advance of the 1942 meetings of the American College of Physicians and the American Medical Association.

During 1942 written examinations will be conducted February 16 and October 19.

OBITUARIES

DR. JAMES ELY TALLEY

American medicine has lost a valued friend in the passing of Dr. James Ely Talley, who died July 3, 1941.

Dr. Talley was a pioneer in the field of cardiology, having founded the cardiac clinic at the Graduate School of Medicine of the University of Pennsylvania and likewise serving as professor of cardiology there from 1921 until he retired in 1938.

He was also one of the founders of the American Heart Association and of the Children's Heart Hospital. Dr. Talley devoted much of his time and tireless energy to both of these enterprises and was always looking forward to a new era when heart disease would remove fewer people from occupations and the mortality rate would be decreased to a minimum.

On receiving his M.D. from the University of Pennsylvania in 1892, Dr. Talley entered general practice in West Philadelphia. In 1905 he carried on postgraduate study in Berlin; in 1911 he studied in London under Sir James MacKenzie and again in London in 1913 under Sir Thomas Lewis.

Being a splendid organizer and possessing the ability of reaching his goal, Dr. Talley served in the World War as Lieutenant Commander and in 1919 after being promoted to Commander, Medical Corps, United States Navy, he helped to establish the U. S. Navy Base Hospital No. 5, at Brest, France.

Dr. Talley has been a Fellow of the American College of Physicians since 1923. Being active in several medical societies, his wise counsel and good fellowship will be missed by his many colleagues. He has offered much to the profession by his many articles dealing with internal medicine and cardiology which appeared in various medical journals.

Dr. Talley was born at Kennett Square, Pennsylvania, July 22, 1864, and died at his home in Lima, Delaware County. He is survived by his wife, Isabella, and two nephews, Robert H. and John H. Andrews. Although he was ill for some time, his death is acknowledged with much regret.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. JULIUS FRIEDENWALD

Dr. Julius Friedenwald was born in Baltimore, December 20, 1866. He died at his home in Baltimore, June 8, 1941.

He was a member of the family of Friedenwalds which for two generations has contributed an outstanding part to the medical and cultural life of Baltimore. He was a specialist in Gastroenterology and contributed many important clinical observations to his particular field. He not only pursued his studies in America, but did a great deal of work abroad. He belonged to all the leading medical societies of this country and also published many

papers. He was the co-author of "Diet in Health and Disease," "Dietetics for Nurses," "Secondary Gastrointestinal Disorders," and also contributed to Tice's "Practice of Medicine."

However, the measure of the man could be obtained only from direct contact with him in his daily work. It has been my good fortune to have known the second generation of Friedenwalds, and as an interne to have worked with Dr. Julius Friedenwald. It was apparent that Dr. Friedenwald was more than a specialist, rather in addition a great physician, practicing not only the science of medicine but also the art of medicine, and always equal to any emergency. Equally important was his active interest in the training of young men. For years he regularly invited the younger men to his home for informal discussion of medical problems, and the Julius Friedenwald Fund for research is a memorial to his zeal for research.

His enviable heritage of culture manifested itself in his extramedical activities, in the musical life of Baltimore, and in his interest in charity, both here and in Palestine.

In the passing of Julius Friedenwald, Baltimore medicine has lost one of its medical landmarks. He was loved and respected by all who knew him, and his spirit shall live on through his many pupils.

Louis Krause, M.D., F.A.C.P.,
Governor for the State of Maryland

DR. HENRY SAMUEL KIESER

Dr. Henry Samuel Kieser, born in Reading, Pennsylvania, July 12, 1903, died very suddenly on July 11, 1941.

Since leaving Hahnemann Medical College in 1930, Dr. Kieser had been primarily interested in Pediatrics. He was Associate in Pediatrics at the Reading Hospital from 1933 to 1938, and also Chief of Pediatrics at the Reading Hospital. He has likewise been Director of Health, Reading Public School System, since 1933.

Dr. Kieser was an energetic and studious young physician with a brilliant future. He had been, for the past year, pursuing graduate work in Pediatrics at the Henry Ford Hospital.

Dr. Kieser was a Diplomate of the American Board of Pediatrics, a member of the Medical Society of the State of Pennsylvania, and a Fellow of the American Medical Association. He had been an Associate of the American College of Physicians since 1940.

Possessing native ability and a pleasing personality, Dr. Kieser was held in esteem by his colleagues and friends, who are shocked by his untimely death.

Edward L. Bortz, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. ALEXANDER S. DEWITT

Dr. Alexander S. DeWitt, F.A.C.P., Detroit, died January 2, 1941. He was born in Amsterdam, Holland, in 1882. At an early age he came to this country and obtained his medical training at the University of Michigan Homeopathic Medical School, receiving his degree in 1905. Thereafter, he spent three and one-half years in postgraduate study in Germany and Austria. He was formerly Associate Professor of Medicine at the Detroit College of Medicine, Associate Attending Physician at Grace Hospital, and for many years Attending Physician at the Providence Hospital. He was a member of the Wayne County Medical Society, Michigan State Medical Society, the American Medical Association, and had been a Fellow of the American College of Physicians since 1920.

DR. F. CLIFTON MOOR

Dr. F. Clifton Moor, F.A.C.P., Tallahassee, Florida, died February 18, 1941, at the age of 61. He received his Bachelor of Arts degree from the Emory University in 1898 and his degree of Doctor of Medicine from the University of Maryland, School of Medicine, in 1903. For many years Dr. Moor was Chief Physician at the Florida State College for Women, and since 1935 had been Director of Student Health and Chief Physician to the Infirmary at this College. He was formerly Mayor of the City of Tallahassee, and had taken a very active interest in civic affairs.

Dr. Moor was a member, past president and secretary of the Leon-Gadsden-Liberty-Wakulla-Jefferson Counties Medical Society, a member and past president of the Florida Medical Association, a member of the Southern Medical Association, a Fellow of the American Medical Association, serving as a member of the House of Delegates during 1934, and had been a Fellow of the American College of Physicians since 1929.

DR. FRED ELLSWORTH CLOW

Dr. Fred Ellsworth Clow, Wolfeboro, New Hampshire, died January 4, 1941 of heart disease. He was born October 25, 1881, and graduated from Harvard Medical School in 1904. He pursued postgraduate work at the National Heart Hospital and the Brompton Hospital, London, England, and at the Massachusetts General Hospital in Boston, and at the New York Post-Graduate Hospital, New York City.

For many years Dr. Clow was a member of the New Hampshire State Board of Registration, Visiting Physician to the Huggins Hospital, Trustee of the New Hampshire State Sanatorium for Tuberculosis, and Consulting Physician to the New Hampshire Soldiers Home. He published several articles in leading medical journals, and was a former President of the Carroll County Medical Society. In addition, he was a member of the New

Hampshire State Medical Society, a Fellow of the American Medical Association, a Diplomate of the American Board of Internal Medicine, and had been a Fellow of the American College of Physicians since 1934.

DR. DORAN J. STEPHENS

Dr. Doran J. Stephens (Associate, 1938) died March 19, 1941. Dr. Stephens was born in 1903, and received the degree of Bachelor of Arts from the University of Rochester in 1926. He then entered the Medical School of that institution and graduated with the M.D. degree in 1929. He interned at the Strong Memorial Hospital of the University of Rochester for two years, was Resident Physician at Barnes Hospital, St. Louis, from 1931 to 1932, and at the same time was an Assistant in Medicine in the Washington University School of Medicine. He then returned to Rochester, New York, where he became Instructor in Medicine at his Alma Mater, and with this institution he was still associated as Assistant Professor of Medicine at the time of his death. He was also Assistant Physician to the Strong Memorial Hospital in Rochester.

Dr. Stephens was a member of Phi Beta Kappa, Sigma Xi, Alpha Omega Alpha, American Society for Clinical Investigation, Society for Experimental Biology and Medicine, the Monroe County Medical Society, the New York State Medical Society, the American Medical Association, and the Rochester Pathological Society. He had been an Associate of the American College of Physicians since 1938.

His scientific work and investigation which included 45 titles was begun during his medical course and later carried into many fields. His last contribution, "The Effects of Pituitrin in Oil," was read before a medical society in Atlantic City during May in *absento de mortem*.